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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

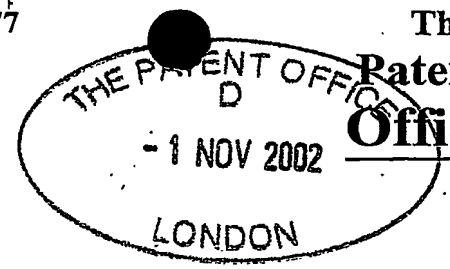
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Stephen Hurdle.

Dated 11 September 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)



The Patent Office

1/77

04NOV02 E760514-1 D01030
P01/7700 0.00-0225548.7

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — DES/HG/P33137

2. Patent application number
(The Patent Office will fill in his par — 0225548.7 — 01 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

08202193 004

United Kingdom

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

07960982

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	49
Claim(s)	1
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 1-Nov-02

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed tf it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

COMPOUNDS

This invention relates to phenyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of prostaglandin mediated diseases.

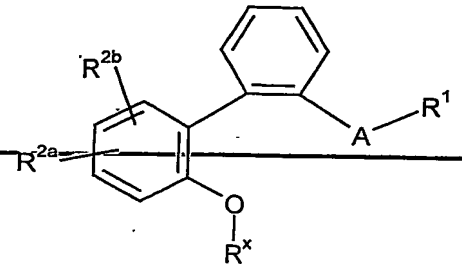
The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology* (1994, 112, 735- 740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation* (2001, 107 (3), 325) shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor.

WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:

A represents optionally substituted phenyl, an optionally substituted 5- or 6- membered heterocyclyl ring or an optionally substituted bicyclic heterocyclyl group;

R^1 represents hydrogen, CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, optionally substituted SO_2C_{1-6}alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, $CONR^5R^6$, 2*H*-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;

wherein when A is a 6-membered ring the R^1 and phenyl group are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 and phenyl group are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

R^{2a} and R^{2b} independently represent hydrogen, halo, CF_3, optionally substituted C_{1-6}alkyl, CN, SO_2R^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted C_{1-8}alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O or SO_n, wherein n is 0, 1 or 2; or R^x may be optionally substituted CQ_2-heterocyclyl or optionally substituted CQ_2Ph wherein Q is independently selected from H and CH_3;

R^4 represents hydrogen or an optionally substituted C_{1-6}alkyl;

R^5 represents hydrogen or an optionally substituted C_{1-6}alkyl;

R^6 represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted SO_2aryl, optionally substituted SO_2heterocyclyl group, CN or COR^7;

R^7 represents optionally substituted aryl or heteroaryl;

or pharmaceutically acceptable derivatives thereof.

Preferably A is selected from an optionally substituted phenyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl; more preferably A is an optionally substituted phenyl or pyridyl. Most preferably A is phenyl optionally substituted by F, Cl, NH_2, NHCOPh, $NHSO_2C_{1-6}$alkyl, or $NHCOC_{1-6}$alkyl.

Preferably R^1 represents CO_2R^4, $CONHSO_2$aryl, $CH_2CO_2R^4$, SO_2NHCOR^7,

SO_2NHCOC_{1-6}alkyl or tetrazolyl. More preferably R^1 represents CO_2R^4. Most preferably R^1 represents CO_2H.

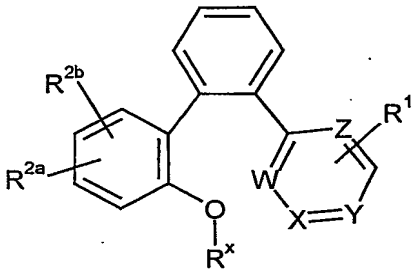
Preferably when A is a 6-membered ring the R^1 and phenyl group are attached to carbon atoms positioned 1,2- or 1,3- relative to each other;

Preferably R^{2a} is hydrogen.

Preferably R^{2b} represents hydrogen, halo, CF_3, optionally substituted C_{1-6}alkyl, CN or -SO_2C_{1-6}alkyl, more preferably R^{2b} represents hydrogen, halo, or CF_3.

Preferably R^x represents an optionally substituted C_{1-6}alkyl, optionally substituted CH_2Ph, CH_2pyridyl, or CH_2thienyl, more preferably C_{1-6}alkyl, optionally substituted CH_2Ph or CH_2thienyl, most preferably R^x represents C_{1-6}alkyl or optionally substituted CH_2Ph.

Preferred compounds of formula (I) are compounds of formula (Ia):



(Ia)

wherein:

R^1 is CO_2R^4, $CONHSO_2Ph$, $CH_2CO_2R^4$, $SO_2NHCOPh$,
SO_2NHCOC_{1-6}alkyl or tetrazolyl;

R^{2a} and R^{2b} are independently selected from hydrogen, halo, or CF_3;

R^x represents optionally substituted C_{1-8}alkyl, or R^x may be optionally substituted CQ_2-heterocyclyl or optionally substituted CQ_2-phenyl wherein Q is independently selected from H and CH_3;

R^4 is hydrogen or an optionally substituted C_{1-6}alkyl;

W, X, Y and Z represents CH or N wherein at least one of W, X, Y or Z is CH;

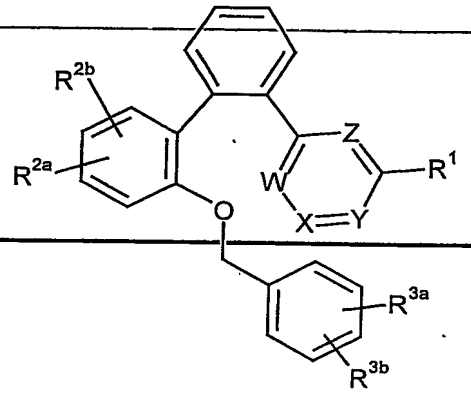
or pharmaceutically acceptable derivatives thereof.

Preferably W, X, Y and Z are each CH.

Preferably R^x is C_{1-8}alkyl or optionally substituted CH_2-Ph.

Preferably R^4 is hydrogen.

More preferably compounds of formula (I) are compounds of formula (Ib):



(Ib)

R^1 is CO_2R^4;

R^{2a} and R^{2b} are independently selected from hydrogen, halo, optionally substituted C_{1-6}alkyl, CF_3, CN or SO_2C_{1-6}alkyl;

R^{3a} and R^{3b} are independently selected from hydrogen, halo or optionally substituted OC_{1-6}alkyl;

R^4 is hydrogen or an optionally substituted C_{1-6}alkyl, preferably hydrogen;

W, X, Y and Z represents CH or N wherein at least one of W, X, Y or Z is CH;

or pharmaceutically acceptable derivatives thereof.

Preferably R^{3a} and R^{3b} independently represent hydrogen, halo or optionally substituted $O(C_{1-6})$alkyl, more preferably hydrogen or halo.

Preferably W, X, Y and Z each represents CH.

Examples of compounds of formula (I) are:

2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-3"-carboxylic acid;

(2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-3"-yl)-acetic acid;

(2-benzyloxy-5-chloro[1,1';2',1"]terphenyl-2"-yl)acetic acid;

(2-benzyloxy-5-chloro[1,1';2',1"]terphenyl-4"-yl)acetic acid;

5"-acetylamino-2-benzyloxy-5-chloro[1,1';2',1"]terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-propionylamino[1,1';2'1"]terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-(2-methylpropanoylamino)-[1,1';2',1"]terphenyl-3"-carboxylic acid;

2-benzoyloxy-5"-butyrylamino-5-chloro[1,1';2',1"]terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-[(1-phenyl-methanoyl)amino]-[1,1';2',1"]terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-dimethanesulfonylamino-[1,1';2',1"]terphenyl-3"-carboxylic acid

5"-amino-2-benzyloxy-5-chloro[1,1';2',2"]-3"-carboxylic acid;

2-benzyloxy-5"-butyrylamino-5-trifluoromethyl[1,1';2',1"]terphenyl-3"-carboxylic acid-3-carboxylic acid;

2-benzyloxy-4"-chloro[1,1';2',1"]terphenyl 2"-carboxylic acid;

2-benzyloxy-5"-fluoro-[1,1';2',1"]terphenyl-2"-carboxylic acid;

2-benzyloxy-4"-fluoro-[1,1';2',1"]terphenyl-2"-carboxylic acid;

2"-benzyloxy-5-fluoro-[1,1';2',1"]terphenyl-3-carboxylic acid;

4"-amino-2-benzyloxy-[1,1';2',1"]terphenyl-3"-carboxylic acid;

5"-acetylamino-2-benzyloxy-[1,1';2',1"]terphenyl-2"-carboxylic acid;
2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-2"-carboxylic acid;
2-benzyloxy-[1,1';2',1"]terphenyl-3"-carboxylic acid;
2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-2"-carboxylic acid amide;
5-(2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-3"-yl)-1H-tetrazole;
N-[1-(2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-2"-yl)-methanoyl]-benzenesulfonamide;
2-benzyloxy-[1,1';2',1"]terphenyl-4"-sulfonic acid (1-phenyl-methanoyl)-amide;
2-benzyloxy-[1,1';2',1"]terphenyl-4"-sulfonic acid [1-(4-nitro-phenyl)-methanoyl]-amide;
2-benzyloxy-[1,1';2',1"]terphenyl-3"-sulfonic acid acetyl-amide;
5-chloro-2-(3-methyl-butoxy)-[1,1';2',1"]terphenyl-3"-carboxylic acid;
5-chloro-2-(4-fluoro-benzyloxy) -[1,1';2',1"]terphenyl-3"-carboxylic acid;
5-chloro-2-(2,4-difluoro-benzyloxy) -[1,1';2',1"] terphenyl-3"-carboxylic acid;
5-chloro-2-(4-chloro-benzyloxy)-[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-(2-fluoro-4-chloro-benzyloxy) -[1,1';2',1"] terphenyl-3"carboxylic;
5-chloro-2-(4-isobutoxy)-[1,1',2',1"] terphenyl-3"-carboxylic acid;
5-chloro-2-(pyridin-2-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-(pyridin-4-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-(pyridin-3-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-cyclohexylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid;
5-chloro-2-(thiophen-3-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-(thiophen-2-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid;
5-chloro-2-cyclopentylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid;
5-chloro-2-propoxy -[1,1';2',1"] terphenyl-3"-carboxylic acid;
2-butoxy-5-chloro-[1,1';2',1"] terphenyl-3"-carboxylic acid;
5-chloro-2-isopropoxy -[1,1';2',1"] terphenyl-3"-carboxylic acid;
5-chloro-2-isobutoxy-[1,1';2',1"]terphenyl-2"-carboxylic acid;
and pharmaceutically acceptable derivatives thereof.

Preferably compounds are selective for EP_1 over EP_3. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP_1 over EP_3.

The invention is described using the following definitions unless otherwise indicated.

The term 'pharmaceutically acceptable derivative' means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of

compounds of formula (I) and the physiological acceptable salts thereof. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms "halogen or halo" are used to represent fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine and bromine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof, for example methylcyclohexyl and methyl cyclopentyl.

The term "alkoxy" as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group.

The term "haloalkyl" means an alkyl group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by

halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. C_{1-6}haloalkyl, for example, includes C_{1-6}fluoroalkyl, e.g. $-CF_3$, $-CHF_2$, $-CF_2CF_3$ and the like.

The term "haloalkoxy" means an alkoxy group, including straight, branched or cyclic structures, of the indicated number of carbon atoms in which one or more hydrogen atoms have been replaced by halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. C_{1-6}Haloalkoxy includes for example C_{1-6}fluoroalkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCF_2CF_3$ and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents. Examples of 5-membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

The term "aryl" as a group or as part of a group means a 5- or 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. Preferably the aryl group is phenyl.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

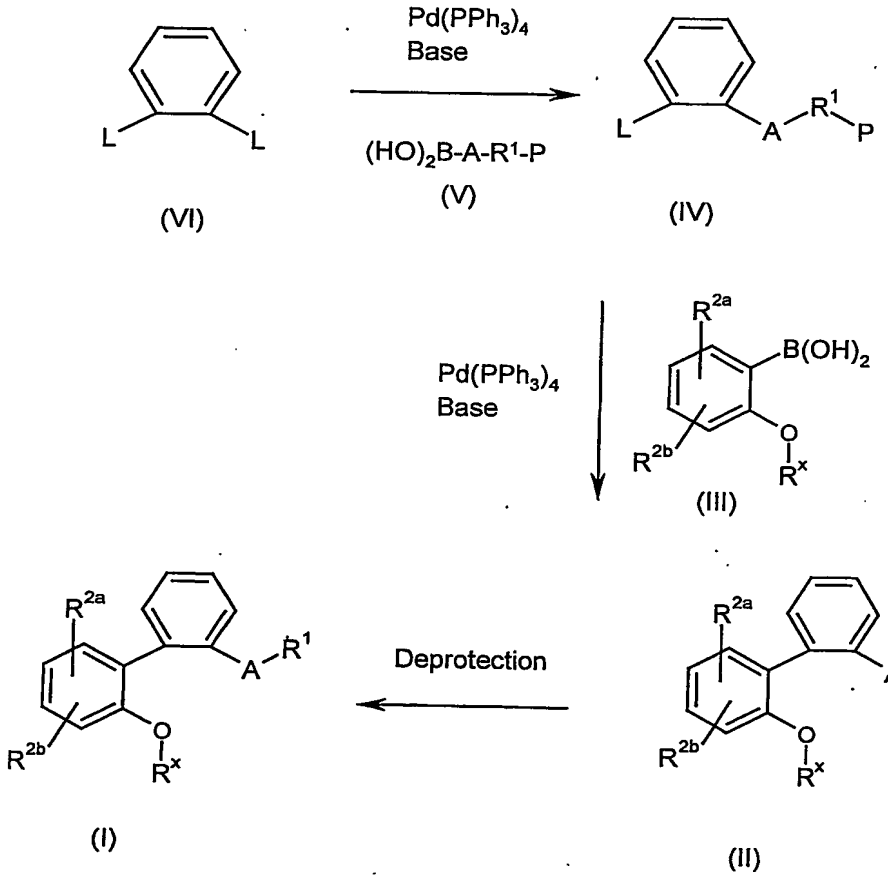
Optional substituents for alkyl or alkenyl groups are OH, CO_2R^4, NR^4R^5, (O), $-OC_{1-6}$alkyl or halo, wherein R^4, R^5 and R^6 are as herein before defined.

Optional substituents for A, aryl, heteroaryl or heterocyclyl groups, unless hereinbefore defined, include one or two substituents selected from halogen; optionally substituted C_{1-6}alkyl; optionally substituted C_{1-6}alkoxy; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; C_{1-6}haloalkyl; C_{1-6}haloalkoxy; NO_2; CN; NR^4R^5; $CONR^4R^5$; $SO_2NR^4R^5$; optionally substituted SO_nC_{1-6}alkyl; optionally substituted $NR^5(CO)C_{1-6}$alkyl; $NR^5(CO)$aryl optionally substituted by one or two substituents selected from halo, NR^4R^5, C_{1-6}alkyl, and OC_{1-6}alkyl; $NR^5(CO)$heteroaryl optionally substituted by one or two substituents selected from halo, NR^4R^5, C_{1-6}alkyl, and OC_{1-6}alkyl; and optionally substituted $NR^5(SO_2)C_{1-6}$alkyl; wherein n, R^4 and R^5 are as hereinbefore defined.

Preferred optional substituents for A, aryl, heteroaryl or heterocyclyl include halogen; C_{1-6}alkyl; C_{1-6}alkoxy; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{1-6}haloalkyl; C_{1-6}haloalkoxy; NO_2; CN; NR^4R^5; $CONR^4R^5$; $SO_2NR^4R^5$; SO_nC_{1-6}alkyl; $NR^5(CO)C_{1-6}$alkyl; $NR^5(CO)$phenyl; and $NR^5(CO)$heteroaryl; wherein n, R^4 and R^5 are as hereinbefore defined.

When the heteroatom nitrogen replaces a carbon atom in a C_{1-8}alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-8}alkyl, preferably hydrogen and C_{1-6}alkyl, more preferably hydrogen.

Compounds of formula (I) can be prepared as set forth in the following scheme and in the examples.



wherein L is a leaving group for example halo, e.g. bromo; P is a protecting group for example methyl or ethyl esters; and R^{2a}, R^{2b}, R^1 and R^x are as defined for compounds of formula (I).

Suitable reaction conditions for the deprotection of a compound of formula (II) include heating in ethanolic sodium hydroxide solution.

Suitable reaction conditions for the reaction of a compound of formula (VI) with a boronic acid of formula (V), or a compound of formula (IV) with a boronic acid of formula (III) include heating with tetrakis(triphenylphosphine)palladium (0) and an inorganic base, for example potassium carbonate, in a solvent, e.g. ethylene glycol dimethyl ether (DME), toluene and ethanol, preferably in a ratio of 1:1.

It will be appreciated that certain substituents in intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art.

Phenyl derivatives of formula (VI), boronic acids of formula (III) and (V), and tetrakis(triphenylphosphine)palladium (0) are commercially available, or readily prepared by methods known to those skilled in the art.

The preparation and reactions of boronic acids of formula (III) and formula (V) is reviewed in Suzuki *et al*, *Synth. Commun.*, 1981, 11, 513; Martin *et al*, *Acta. Chim. Scand.*, 1993, 47, 221; and Miyaura *et al*, *Chem. Rev.*, 1995, 95, 2457. For example, 2-benzyloxy-5-chlorophenylboronic acid may be prepared from 2-benzyloxy-5-chloro-iodobenzene. 2-Benzyloxy-5-chloro-iodobenzene may be prepared from 4-chloro-2-iodoanisole by demethylation followed by benzylation according to known methods.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and are therefore useful in treating EP_1 receptor mediated diseases.

In view of their ability to bind to the EP_1 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain

associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful in the treatment of bone disease characterised by abnormal bone metabolism or resorbtion such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also useful in the treatment of tinnitus.

The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

~~According to a further aspect of the invention, we provide a compound of formula (I) or a~~ pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US 5,474,995 US 5,633,272; US 5,466,823, US 6,310,099 and US 6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO 99/12930, WO 00/26216, WO 00/52008, WO 00/38311, WO 01/58881 and WO 02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

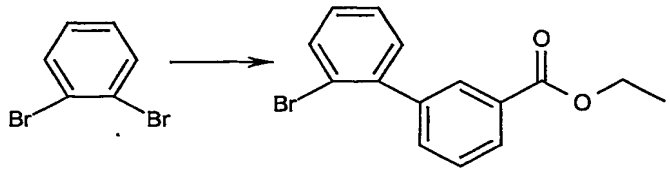
EXAMPLES

Abbreviations:

EDC 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
THF tetrahydrofuran
DMSO dimethyl sulfoxide
DCM dichloromethane
DMF N,N-dimethylformamide

Example 1: 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-carboxylic acid

a) 2'-Bromo-biphenyl-3-carboxylic acid ethyl ester

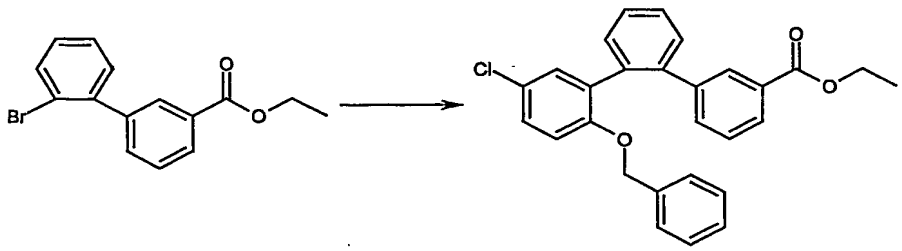


A mixture of 1,2-dibromobenzene (0.63ml, 5.2mmol), (3-ethoxycarbonylphenyl)boronic acid (506mg, 2.6mmol), tetrakis(triphenylphosphine)palladium(0) (640mg, 0.6mmol) and potassium carbonate (2.879g, 20.9mmol, 8 equivalents) was heated in toluene-ethanol (1:1, 10ml, 0.01M) at 90°C for 3 hours. Upon cooling, the mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated.. The residue was purified by chromatography using Biotage with iso-hexane containing a gradient of DCM (2-15%) to yield the title compound (538mg, 34%).

^{1}H NMR ($CDCl_3$) 1.40 (3H, t, J=7Hz), 4.40 (2H, q, J=7Hz), 7.20-7.25 (1H, m), 7.30-7.40 (2H, m), 7.50 (1H, t, J=8Hz), 7.62 (1H, br d, J=7Hz), 7.68 (1H, d, J=8Hz), 8.05-8.10 (2H, m).

R_f 0.31 (5% EtOAc in iso-hexane).

b) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester



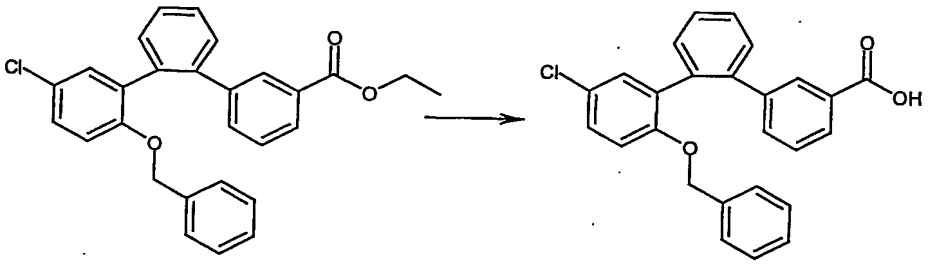
2'-Bromo-biphenyl-3-carboxylic acid ethyl ester (157mg, 0.5mmol), 2-benzyloxy-5-chloro-phenylboronic acid (157mg, 0.6mmol), tetrakis(triphenylphosphine)palladium(0) (66mg, 0.06mmol) and potassium carbonate (568mg, 4.1mmol, 8 equivalents) was heated in toluene-ethanol (1:1, 5ml) at 90°C for 4.5 hours. Upon cooling, the mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography using Biotage with iso-hexane containing a gradient of ethyl acetate (1-5%) to yield the title compound (105mg, 46%) as a white solid.

^{1}H NMR ($CDCl_3$) (3H, t, J=7Hz), 4.28 (2H, q, J=7Hz), 4.50-4.80 (2H, br. s), 6.60 (1H, d, J=9Hz), 6.94-6.98 (2H, m), 7.10 (1H, dd, J=3Hz, J=9Hz), 7.18-7.25 (6H, m's excess), 7.35-7.50 (4H, m), 7.83 (1H, s), 7.88 (1H, dt, J=1Hz, J=7.5Hz).

R_f 0.15 (5% EtOAc in iso-hexane).

LC/MS t = 4.23 (100%), [MH+] 443.

c) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-carboxylic acid



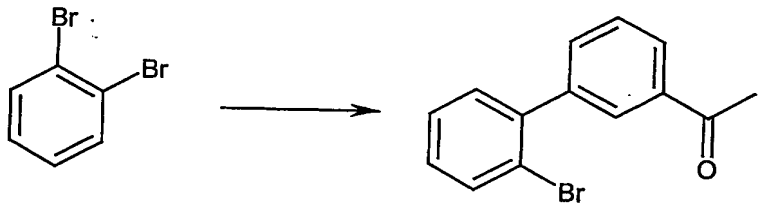
2-Benzyloxy-5-chloro-[1,1',2,2']terphenyl-3"-carboxylic acid ethyl ester (103mg, 0.2mmol) was heated at 90°C in ethanol (2ml) containing 2M sodium hydroxide (1ml) in a reacti-vial for 2 hrs. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with 2M HCl, dried (Na_2SO_4), filtered and concentrated to yield the title compound (82mg, 85%).

^{1}H NMR ($CDCl_3$) 4.52-4.82 (2H, br. s), 6.62 (1H, d, J=9Hz), 6.99 (2H, m), 7.12 (1H, dd, J=3Hz, J=8.5Hz), 7.18-7.30 (6H, m's excess), 7.36-7.50 (4H, m), 7.90-7.95 (2H, m).

LC/MS t =3.97 (100%), [MH-] 413, 415.

Example 2: (2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-yl)-acetic acid

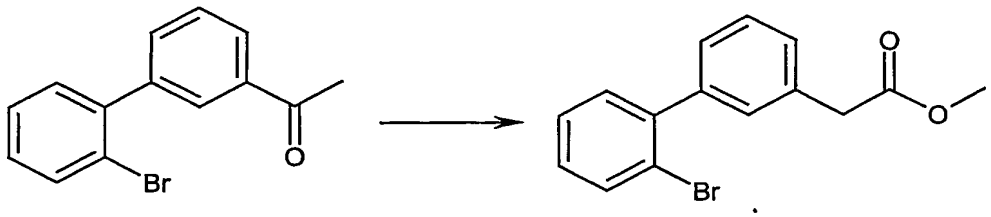
a) 1-(2'-Bromo-biphenyl-3-yl)-ethanone



A mixture of 3-acetylphenylboronic acid (1.64 g, 10mmol), 1,2-dibromobenzene (4.72g, 20 mmol), potassium carbonate (6.9 g, 50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.58 g, 0.5 mmol) in 1:1 toluene/ethanol (40 ml) was stirred and heated at 90°C under nitrogen for 16 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography using Biotage

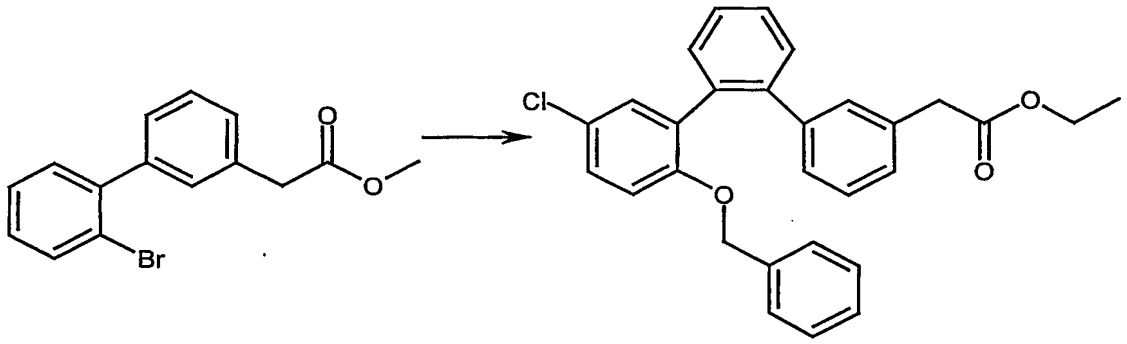
with iso-hexane containing a gradient of dichloromethane (20-50%) to yield the title compound as a white solid (1.74 g 63%).
^{1}H NMR ($CDCl_3$) δ: 2.64 (3H, s), 7.24-7.39 (3H, m), 7.52-7.70 (3H, m), 7.98-8.00 (2H, m).
LC/MS t=3.42, [MH+] 276.9.

b) (2'-Bromophenyl-3-yl)-acetic acid methyl ester



Iodine (533 mg, 2.1 mmol) was added to a stirred suspension of 1-(2'-bromo-biphenyl-3-yl)-ethanone (550 mg, 2 mmol) and silver nitrate (714 mg, 4.2 mmol) in methanol (9 ml) and trimethyl orthoformate (3 ml) and the resulting mixture refluxed for 16 hours. After cooling the mixture was filtered, diluted with water and diethyl ether and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified using Biotage with dichloromethane/iso-hexane (3:7) to yield the title compound as a colourless gum (499 mg 82%).
^{1}H NMR ($CDCl_3$) δ: 3.69 (2H, s), 3.71 (3H, s), 7.19-7.39 (7H, s), 7.66 (1H, d, J=8Hz).
LC/MS t=3.49, [MH+] 306.9.

c) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-3''-yl)acetic acid ethyl ester

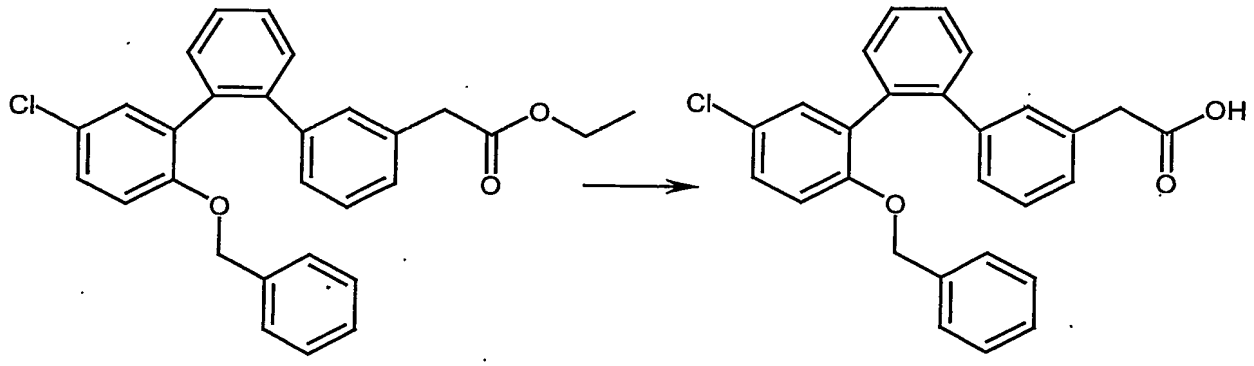


A mixture of (2'-bromo-biphenyl-3-yl)-acetic acid methyl ester (76 mg, 0.25 mmol), 2-benzyloxy-5-chloro-phenyl-boronic acid (72 mg, 0.275 mmol), potassium carbonate (276 mg, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) in 1:1 toluene/ethanol (3 ml) was heated and stirred at 90^{0}C under nitrogen for 2 hours. After cooling the mixture was diluted with

water and diethyl ether and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a colourless gum (112 mg, 98%).

^{1}H NMR ($CDCl_3$) δ: 1.2 (3H, t, J=7Hz), 3.40 (2H, s), 4.06 (2H, q, J=7Hz), 4.66 (2H, br s), 6.59 (1H, d, J=8Hz), 6.96-7.42 (15H, m).

d) (2-Benzyloxy-5-chloro-[1,1';2'1'']terphenyl-3''-yl)-acetic acid



A solution of (2-benzyloxy-5-chloro-[1,1';2'1"]terphenyl-3"-yl)-acetic acid ethyl ester (112 mg, 0.25 mmol) in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2mmol) was stirred at room temperature for 1 hour then diluted with water and 1:1 diethyl ether/iso-hexane. The aqueous suspension was separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic solution was dried ($MgSO_4$) evaporated to dryness and the residue triturated with iso-hexane to give the title compound as a white solid (86 mg, 80%).

^{1}H NMR ($CDCl_3$) δ: 3.56 (2H, s), 4.78 (2H, br s), 6.71 (1H, d, J=8Hz), 7.10-7.59 (15H, m).

LC/MS t=3.86, [MH-] 427, 429

The following compounds were prepared in a similar manner:

Example 3: (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-2''-yl)acetic acid

a) 1-(2'-Bromo-biphenyl-2-yl)-ethanone

^{1}H NMR ($CDCl_3$) δ: 2.36 (3H, s), 7.38-7.91 (8H, m).

LC/MS t=3.31, [MH+]276.9

b) (2'Bromo-biphenyl-2-yl)-acetic acid methyl ester

^{1}H NMR ($CDCl_3$) δ: 3.47 (2H, q), 3.56 (3H, s), 7.16-7.64 (7H, m), 7.65 (1H, d).

c) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-2''-yl)acetic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7Hz), 3.20 (1H, br d), 3.43 (1H, d, J=16Hz), 4.03 (2H, q, J=7Hz), 4.86 (2H, q), 6.61 (1H, d), 6.99-7.40 (15H, m).

d) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-2''-yl)acetic acid

^{1}H NMR ($CDCl_3$) δ: 3.18 (1H, br d), 3.44 (1H, d, J=16Hz), 4.83 (2H, q), 6.60 (1H, d, J=9Hz) 7.02-7.40 (15H, m).

LC/MS t=3.81, [MH-] 427, 429.1

Example 4: (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-4''-yl)acetic acid

a) 1-(2'-Bromo-biphenyl-4-yl)-ethanone

^{1}H NMR ($CDCl_3$) δ: 2.66 (3H, s), 7.25-7.39 (3H, m), 7.52 (2H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 8.03 (2H, d, J=8Hz).

LC/MS t=3.45, [MH+] 274.9

b) (2'Bromo-biphenyl-4-yl)-acetic acid methyl ester

^{1}H NMR ($CDCl_3$) δ: 3.68 (2H, s), 3.73 (3H, s), 7.17-7.40 (7H, m), 7.67 (1H, d, J=8Hz)

c) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-4''-yl)acetic acid ethyl ester

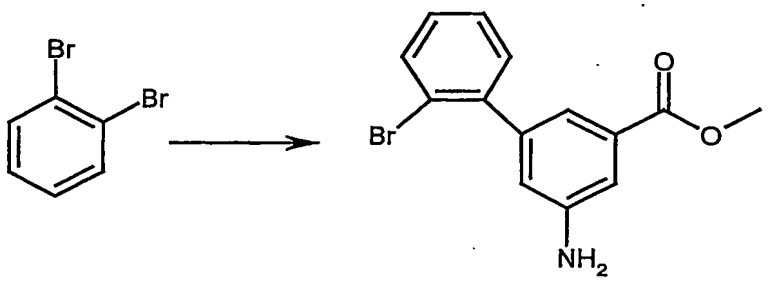
^{1}H NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7Hz), 3.56 (2H, s), 4.14 (2H, q, J=7Hz), 4.64 (2H, br s), 6.61 (1H, d, J=8Hz), 6.99-7.41 (15H, m).

d) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-4''-yl)acetic acid

^{1}H NMR ($CDCl_3$) δ: 3.61 (2H, s), 4.62 (2H, br s), 6.59 (1H, d, J=8Hz), 6.98-7.42 (15H, m).

Example 5: 5''-Acetylamino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid

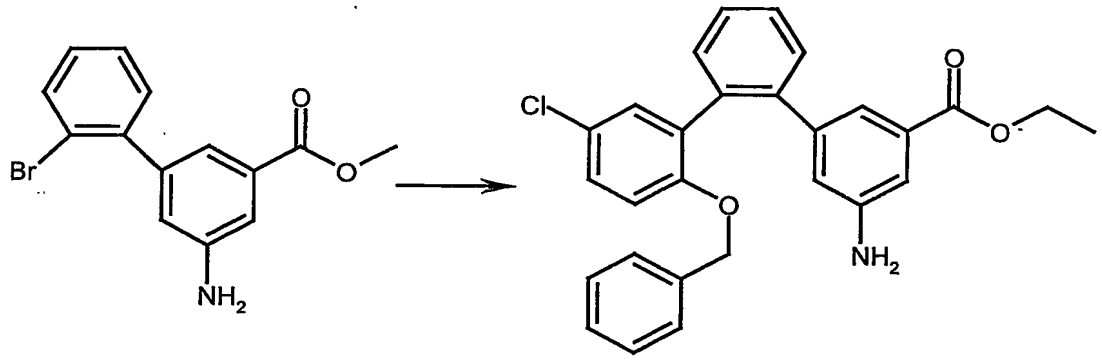
a) 5-Amino-2'-bromobiphenyl-3-carboxylic acid methyl ester



A mixture of (3-amino-5-methoxycarbonylphenyl)boronic acid (1.02 g, 5.23 mmol), 1,2-dibromobenzene (2.47g, 10.46 mmol), potassium carbonate (5.52 g, 40 mmol) and tetrakis(triphenylphosphine)palladium(0) (606 mg, 0.523 mmol) in 1:1 toluene/ethanol (30 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (3:17) to yield the title compound as a colourless gum (1.21g, 76%).

^{1}H NMR ($CDCl_3$) δ: 3.86 (2H, br s), 3.90 (3H, s), 6.90 (1H, s), 7.19-7.38 (4H, m), 7.45 (1H, s), 7.65 (1H, d, J=8Hz).

b) 5''-Amino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

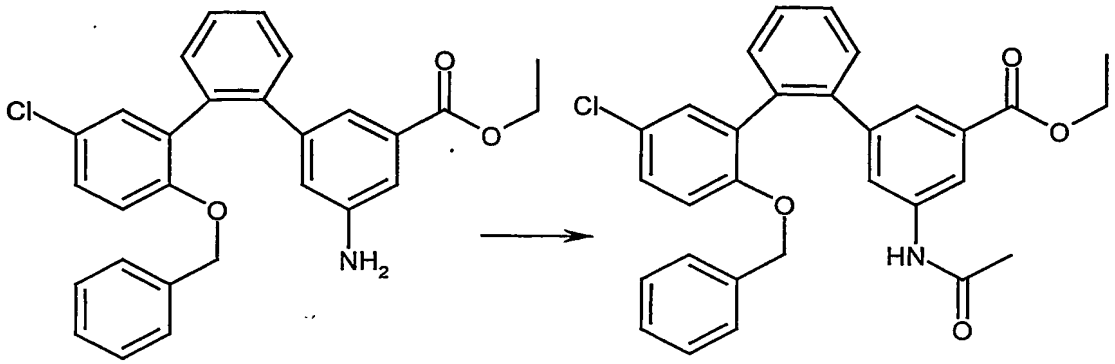


A mixture of 2-benzyloxy-5-chloro-phenyl-boronic acid (197 mg, 0.75 mmol), 5-amino-2'-bromo-biphenyl-3-carboxylic acid methyl ester (216 mg, 0.71 mmol), potassium carbonate (828 mg, 6 mmol) and tetrakis(triphenylphosphine)palladium(0) (79 mg, 0.068mmol) in 1:1 toluene/ethanol (8 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a pale yellow gum. (288 mg, 89%).

^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7Hz), 3.52 (2H, br s), 4.23 (2H, q, J=7Hz), 4.68 (2H, br s), 6.52 (1H, s), 6.63 (1H, d, J=9Hz), 7.00-7.41 (13H, m).

LC/MS t=3.93, [MH+] 458.2, 460.2.

c) 5''-Acetylamino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

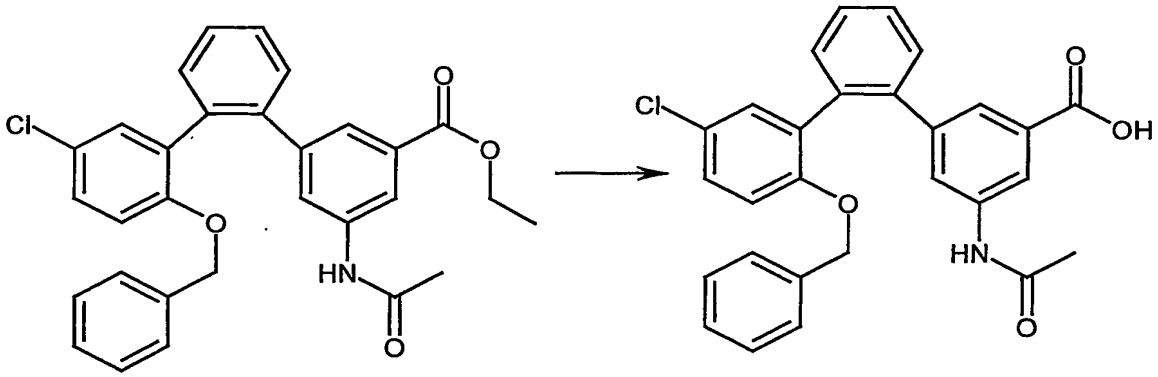


Acetic anhydride (53 mg, 0.5 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (96 mg, 0.21mmol) in pyridine (2 ml) and the mixture left at room temperature for 1 hour. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness to yield the title compound as a colourless gum. (102 mg, 97%).

^{1}H NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7Hz), 2.10 (3H, s), 4.25 (2H, q), 4.70 (2H, br d), 6.63 (1H, d, J=9Hz), 6.99-7.43 (12H, m), 7.50 (1H, s), 8.00 (1H, s).

LC/MS t=3.86, [MH+] 500, 502.1.

d) 5"-Acetylamino-2-benzyloxy-5-chloro[1,1';2',1"]terphenyl-3"-carboxylic acid



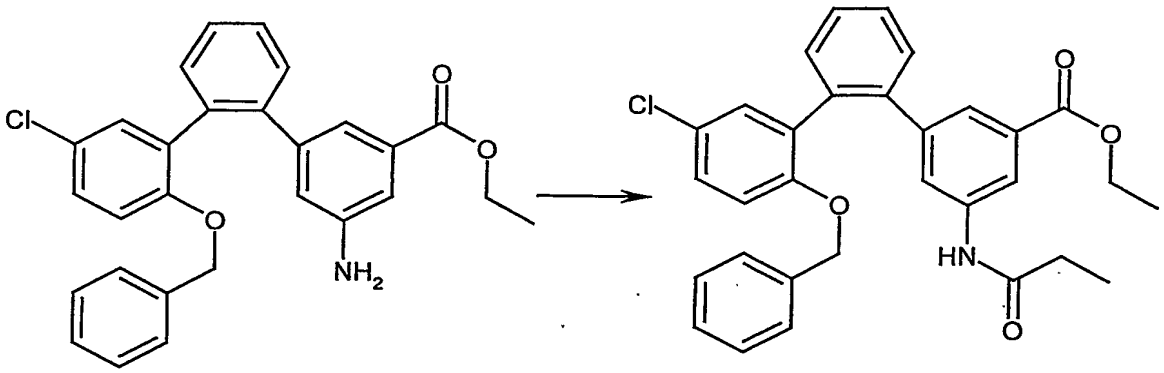
5"-Acetylamino-2-benzyloxy-5-chloro-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (102 mg, 0.2 mmol) was dissolved in a mixture of ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and left at room temperature for 5 hours. The resulting solution was diluted with water, washed with diethyl ether and the aqueous phase separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and evaporated to dryness to yield the title compound as a white solid. (81 mg, 84%).

^{1}H NMR ($CDCl_3$) δ: 2.12 (3H, s), 4.70 (2H, br d), 6.65 (1H, d, J=8Hz), 7.00-7.45 (12H, m) 7.58 (1H, s), 8.07 (1H, s).

LC/MS t=3.59, [MH-] 470.1, 472.1.

Example 6: 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1"]terphenyl-3"-carboxylic acid

a) 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1"]terphenyl-3"-carboxylic acid ethyl ester

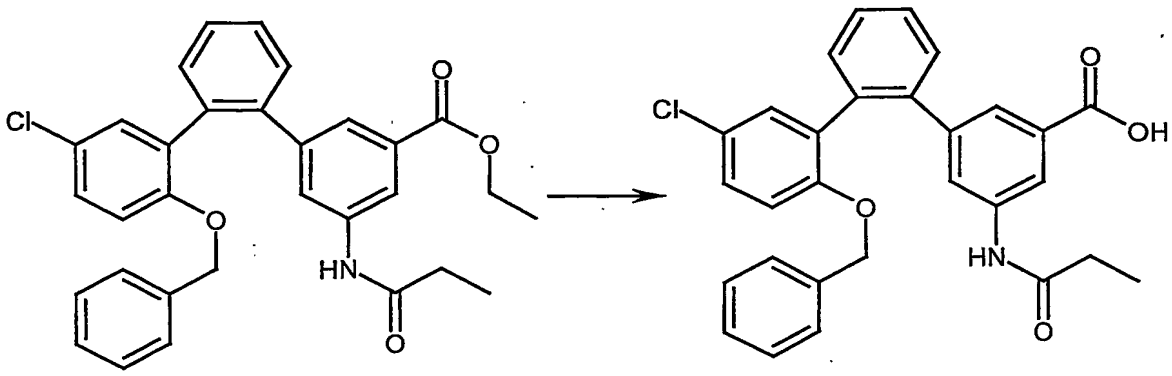


Propionyl chloride (10 mg, 0.11 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (47 mg, 0.1 mmol) and triethylamine (12 mg, 0.12 mmol) in dichloromethane (2 ml) and the mixture left at room temperature for 2 hours. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution then dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:3) to yield the title compound as a colurless gum. (49 mg, 95%).

^{1}H NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7Hz), 1.30 (3H, t, J=7Hz), 2.30 (2H, q, J=7Hz), 4.25 (2H, q, J=7Hz), 4.68 (2H, br d), 6.63 (1H, d, J=9Hz), 6.88 (1H, s), 7.00-7.50 (13H, m), 8.03 (1H, s).

LC/MS t=4.03, [MH+] 514.2, 516.2.

b) 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1"]terphenyl-3"-carboxylic acid



2-Benzyloxy-5-chloro-5"-propionylamino-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (49 mg, 0.095 mmol) was dissolved in ethanol (5 ml) and 1M sodium hydroxide (1 ml, 1 mmol) and left at room temperature for 5 hours. The resulting solution was diluted with water acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) evaporated to dryness and triturated with iso-hexane to yield the title compound as an off-white solid. (31 mg, 67%).

^{1}H NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7Hz), 2.33 (2H, q, J=7Hz), 4.70 (2H, br d), 6.65 (1H, d, J=9Hz), 6.90 (1H, s), 7.03-7.46 (12H, m), 7.57 (1H, s), 8.10 (1H, s).

LC/MS t=3.75, [MH-] 484.3, 486.2.

The following compounds were prepared in a similar manner:

Example 7: 2-Benzyloxy-5-chloro-5"-(2-methylpropanoylamino)-[1,1';2',1"]terphenyl-3"-carboxylic acid

a) 2-Benzyloxy-5-chloro-5"-(2-methylpropanoylamino)-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 1.20 (3H, s), 1.22 (3H, s), 1.30 (3H, t, J=7Hz), 2.42 (1H, m), 4.25 (2H, q, J=7Hz), 4.70 (2H, br d), 6.63 (1H, d, J=9Hz), 6.90-7.50 (14H, m), 8.02 (1H, s).

LC/MS t=4.11, [MH+] 528.3, 530.2.

b) 2-Benzyloxy-5-chloro-5"-(2-methylpropanoylamino)-[1,1';2',1"]terphenyl-3"-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.21 (3H, s), 2.43 (1H, m), 4.70 (2H, br d), 6.66 (1H, d, J=9Hz), 6.91 (1H, s), 7.03-7.47 (12H, m), 7.57 (1H, s), 8.10 (1H, s).

LC/MS t=3.85, [MH-]498.2, 500.2.

Example 8: 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid

a) : 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7Hz), 1.29 (3H, t, J=7Hz), 1.70 (2H, m), 2.26 (2H, t, J=7Hz), 4.25 (2H, q, J=7Hz), 4.70 (2H, br d), 6.63 (1H, d, J= 9Hz), 6.91 (1H, s), 7.01-7.51 (12H, m), 8.02 (1H, s).
LC/MS t=4.12, [MH+] 528.1, 530.1.

b) : 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid
^{1}H NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7Hz). 1.72 (2H, m), 2.27 (2H, t, J=7Hz), 4.71 (2H, br d), 6.65 (1H, d, J=9Hz), 6.87 (1H, s), 7.02-7.46 (12H, m), 7.58 (1H, s), 8.09 (1H, s).
LC/MS t=3.86, [MH-] 498.1, 500.1.

Example 9: 2-Benzyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid

a) 2-Benzyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

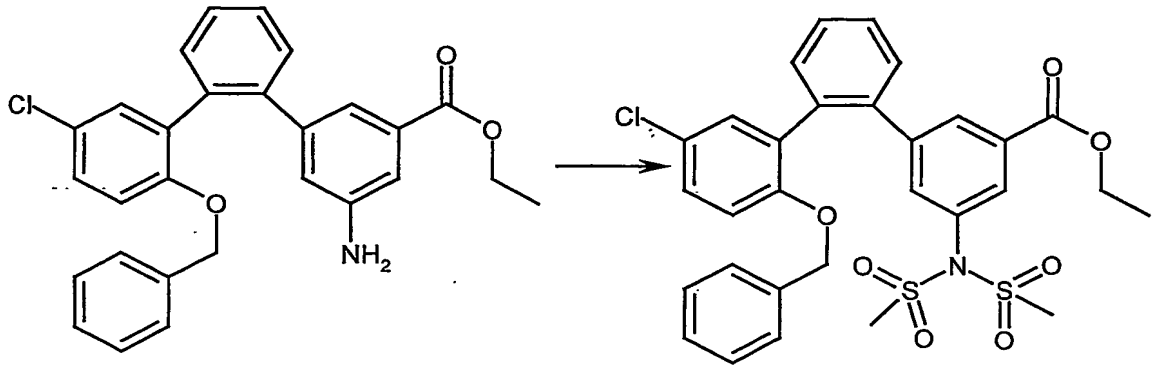
^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7Hz), 4.26 (2H, q, J=7Hz), 4.70 (2H, br d), 6.65 (1H, J=9Hz), 7.02-7.57 (16H, m), 7.79 (2H, m), 8.15 (1H, s).
LC/MS t=4.22, [MH+] 562.2, 564.2.

b) 2-Benzyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 4.70 (2H, br d), 6.67 (1H, d, J=9Hz), 7.04-7.61 (17H, m), 7.80 (2H, d, J=7Hz), 8.23 (1H, s).
LC/MS t=4.01, [MH-] 532.2, 534.3.

Example 10: 2-Benzyloxy-5-chloro-5''-dimethanesulfonylamino-[1,1';2',1'']terphenyl-3''-carboxylic acid

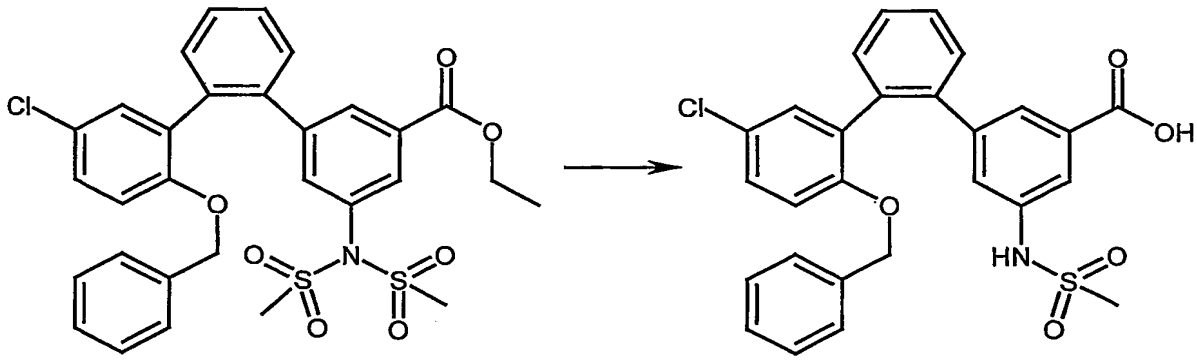
a) 2-Benzyloxy-5-chloro-5''-dimethanesulfonylamino-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester



Methanesulphonyl chloride (25 mg, 0.22 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (47 mg, 0.1 mmol) and triethylamine (25 mg, 0.25 mmol) and the mixture left at room temperature for 3 hours. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution then dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a colurless gum. (56 mg, 91%).

^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7Hz), 3.14 (6H, br d), 4.18 (2H, br s), 4.48 (1H, br d), 4.69 (1H, br d), 6.66 (1H, d, J=9Hz), 6.94-7.51 (12H, m), 7.80 (1H, s), 7.95 (1H, s).

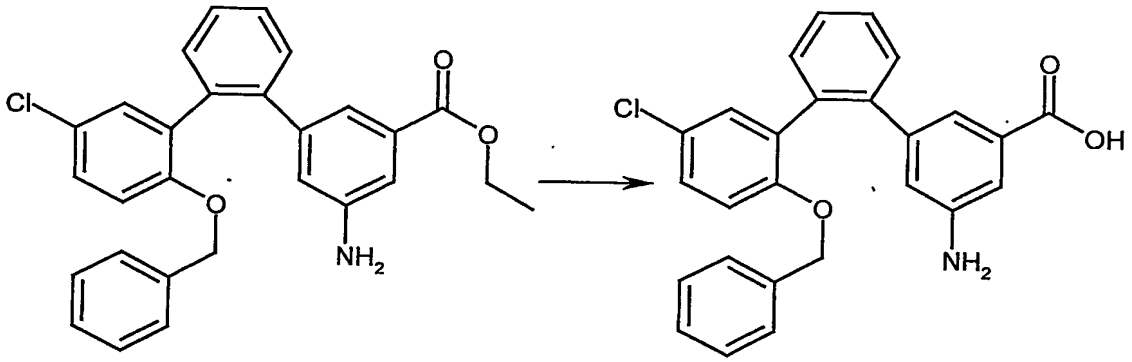
b) 2-Benzyloxy-5-chloro-5"-dimethanesulfonylamino-[1,1';2',1"]terphenyl-3"-carboxylic acid



2-Benzyloxy-5-chloro-5"-dimethanesulfonylamino-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester was dissolved in ethanol (5 ml) and 1M sodium hydroxide (1 ml, 1 mmol) and left at room temperature for 5 hours then heated at 50°C for 1 hour. The resulting solution was diluted with water, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$), evaporated to dryness and triturated with diethyl ether/iso-hexane to yield the title compound as a white solid. (21 mg, 46%).

^{1}H NMR (DMSO-d_6) δ: 2.67 (3H,s), 4.85 (2H, br s), 6.91 (1H, d, J=9Hz), 7.03-7.53 (13H, m), 7.67 (1H, s), 9.87 (1H, s), 12.9 (1H, br s).
LC/MS t=3.68, [MH-] 506.2, 508.2.

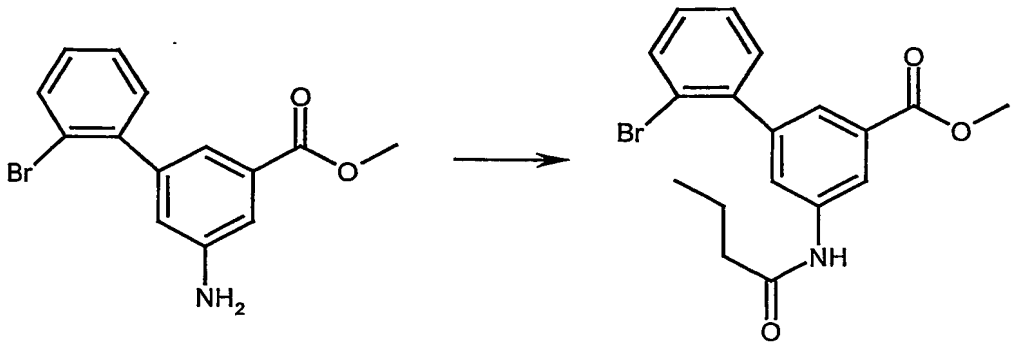
Example 11: 5"-Amino-2-benzyloxy-5-chloro[1,1';2',2"]-terphenyl-3"-carboxylic acid



5"-Amino-2-benzyloxy-5-chloro-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester (192 mg, 0.42 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (2 ml, 4 mmol) and heated at 60°C for 1 hour. The resulting solution was diluted with water acidified with acetic acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) evaporated to dryness and triturated with iso-hexane/diethyl ether to yield the title compound as a white solid. (141 mg, 78%).
^{1}H NMR (DMSO-d_6) δ: 4.9 (2H, br s), 5.23 (2H, br s), 6.58 (1H, s), 6.89 (1H, s), 6.95 (1H, d, J=9Hz), 7.02 (1H, dd, J=9Hz, 2Hz), 7.13 (1H, d, J=9Hz), 7.24-7.41 (10H, m), 12.4 (1H, br s).
LC/MS t=3.59 [MH-] 470.1, 472.1.

Example 12: 2-Benzyloxy-5"-butyrylamino-5-trifluoromethyl[1,1';2',1"]terphenyl-3"-carboxylic acid

a) 2'-Bromo-5-butyrylamino-biphenyl-3-carboxylic acid methyl ester

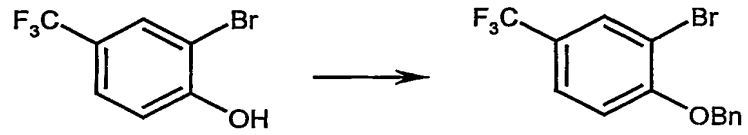


Butyryl chloride (55 mg, 0.52 mmol) was added to a solution of 5-amino-2'-bromo-biphenyl-3-carboxylic acid methyl ester (153 mg, 0.5 mmol) and triethylamine (76 mg, 0.75 mmol) in dichloromethane (5 ml) and the mixture left at room temperature for 30 minutes. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate, dried ($MgSO_4$) and evaporated to dryness to yield the title compound as a light yellow gum. (161 mg, 88%).

^{1}H NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7Hz), 1.77 (2H, m), 2.37 (2H, t, J=7Hz), 3.92, (3H,s), 7.20-7.36 (3H, m), 7.43 (1H, br s), 7.66 (1H, d, J=8Hz), 7.83 (1H, s), 7.94 (1H, s), 8.10 (1H, s).

LC/MS t=3.54, [MH+] 378.

b) 4-Benzyloxy-3-bromobenzotrifluoride

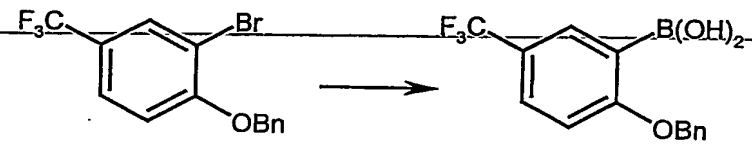


A solution of 3-bromo-4-hydroxybenzotrifluoride (6.03g, 25mmol) in acetone (100ml) was treated with benzyl bromide (4.67g, 3.25ml, 27.5mmol) and potassium carbonate (5.18g, 37.5mmol). The mixture was stirred and heated to reflux under nitrogen for 2h. After cooling, diethyl ether (300ml) and water (300ml) were added and the aqueous phase re-extracted with diethyl ether (100ml). The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The orange oil was flash chromatographed (silica gel, 2-5% dichloromethane-isohexane) to give the title compound as a clear oil (7.0g, 85%).

^{1}H NMR ($CDCl_3$) δ: 5.22 (2H,s), 6.98 (1H, d, J = 9Hz), 7.34-7.51 (6H, m), 7.83 (1H, s).

The product contains a trace impurity that can be removed by recrystallisation from isohexane at –78°C.

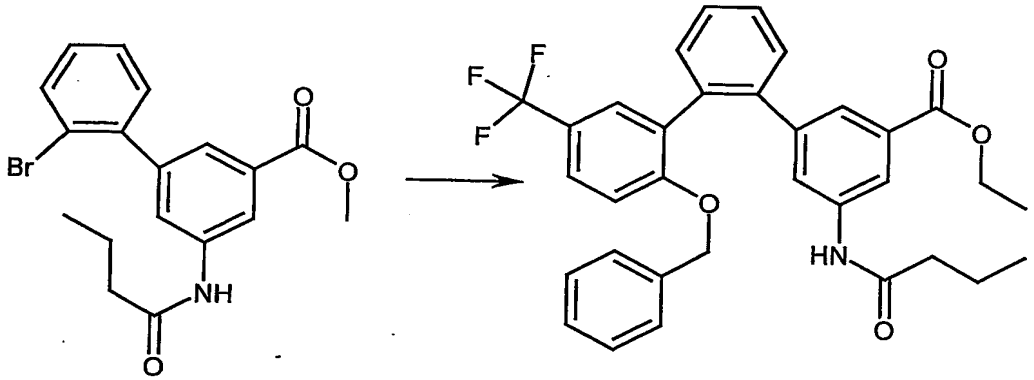
c) 2-Benzyloxy-5-trifluoromethylbenzeneboronic acid



A solution of 4-benzyloxy-3-bromobenzotrifluoride (4.48g, 13.54mmol) in tetrahydrofuran (100ml) was cooled to –100°C (diethyl ether/liquid nitrogen) with stirring under nitrogen. 1.6M n-butyllithium in hexanes (9.3ml, 14.89mmol) was added over 20mins. at –100°C and the mixture warmed to –78°C (acetone/Drikold) and stirred for 1h. Triisopropylborate (7.64g, 9.38ml, 40.66mmol) was added dropwise at –78°C and the reaction stirred and allowed to warm to room temperature over 1.5h. 1M Hydrochloric acid (100ml) was added and the mixture stirred vigorously for 1h. The layers were separated and the aqueous layer extracted with diethyl ether (50ml). The combined organic phases were washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The yellow waxy solid was flash chromatographed (silica gel, 4-20% EtOAc-isohexane) and the product triturated with hexane. The white solid was filtered and dried *in vacuo* to give the title compound (1.53g, 38%).

^{1}H NMR ($CDCl_3$) δ: 5.20 (2H, s), 5.76 (2H, s), 7.05 (1H, d, J = 9Hz), 7.42-7.44 (5H, m), 7.68 (1H, dd J = 2Hz, J = 9Hz), 8.15 (1H, s).

d) 2-Benzyloxy-5''-butyrylamino-5-trifluoromethyl[1,1';2',1'']terphenyl-3''-carboxylic acid

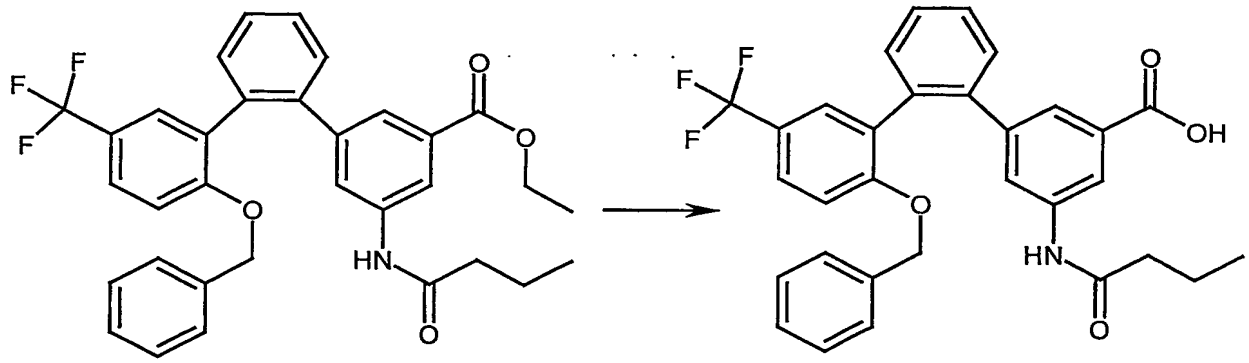


A mixture of 2-benzyloxy-5-trifluoromethyl-phenyl-boronic acid (38 mg,0.13 mmol), 2'-bromo-5-butyrylamino-biphenyl-3-carboxylic acid methyl ester (45 mg, 0.12 mmol), potassium carbonate (138 mg, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol) in 1:1 toluene/ethanol (3 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a colourless gum (51 mg, 76%).

^{1}H NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7Hz), 1.26 (3H, t, J=7Hz), 1.71 (2H, m), 2.25 (2H, t, J=7Hz), 4.23 (2H, q, J=7Hz), 6.75 (1H, d, J=8Hz), 6.89 (1H, s), 7.02 (2H, m) 7.24-7.47 (11H, m), 7.51 (1H, s), 7.97 (1H, s).

LC/MS t=4.13, [MH-] 560.2.

e) 2-Benzyloxy-5''-butyrylamino-5-trifluoromethyl[1,1';2',1'']terphenyl-3''-carboxylic acid

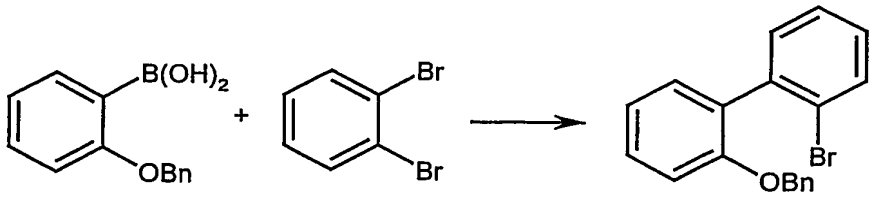


2-Benzyloxy-5''-butyrylamino-5-trifluoromethyl-[1,1',2',1'']terphenyl-3''-carboxylic acid ethyl ester (51 mg, 0.091 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and left at room temperature for 18 hours. The resulting solution was diluted with water acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) evaporated to dryness and triturated with iso-hexane to yield the title compound as an off-white solid. (40 mg, 83%).

^{1}H NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7Hz), 1.71 (2H, m), 2.26 (2H, t, J=7Hz), 4.82 (2H, br s), 6.78 (1H, d, J=9Hz), 6.88 (1H, s), 7.04 (2H, d, J=7Hz), 7.25-7.48 (10H, m), 7.54 (1H, s), 8.03 (1H, s).
LC/MS t=3.87, [MH-] 532.2.

Example 13: 2-Benzyloxy-4''-chloro[1,1';2',1'']terphenyl 2''-carboxylic acid

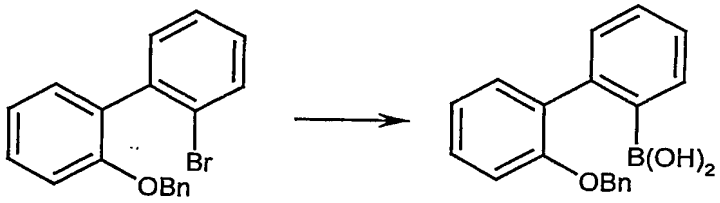
a) 2'-Benzyloxy-2-bromobiphenyl



A solution of 2-benzyloxyphenylboronic acid (4.3g. 19.3mmol) and 1,2-dibromobenzene (9.11g, 4.66ml, 38.6mmol) in 1:1 toluene: ethanol (150ml) was stirred under nitrogen and tetrakis(triphenylphosphine)palladium(0) (1.12g, 0.95mmol) and potassium carbonate (21.3g, 154mmol) added. The reaction was stirred at 90°C under nitrogen for 2 hours. After cooling, diethyl ether (100ml) and water (100ml) were added and the organic phase separated. The aqueous phase was extracted with diethyl ether (50ml) and the combined organic layers washed with water,

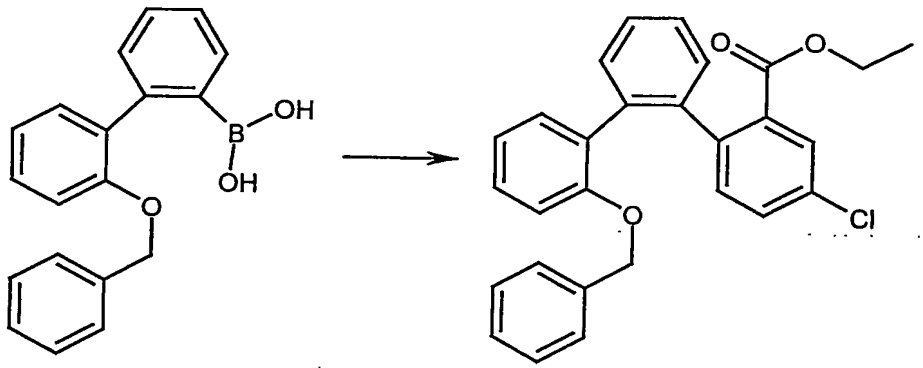
dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was flash chromatographed (silica gel, 5-15% CH_2Cl_2-isohexane) to give the title compound as a clear oil (4.53g, 69%).
^1H NMR ($CDCl_3$) δ: 5.07 (2H, s), 7.02 (2H, m), 7.19-7.34 (10H, m), 7.65 (1H, d, J = 8Hz).

b) 2'-Benzyloxy-biphenyl-2-boronic acid



A solution of 2'-benzyloxy-2-bromobiphenyl (2.41g, 7.09mmol) in tetrahydrofuran (50ml) was stirred under nitrogen and cooled to –100°C (diethyl ether/liquid nitrogen). 1.6M ^{n}Butyllithium in hexanes (4.87ml, 7.80mmol) was added over 15 mins. at –100°C and the mixture warmed to –78°C (acetone/Drikold) and stirred for 1h. Triisopropyl borate (4.00g (5.02ml, 21.30mmol) was added at –78°C and the reaction allowed to warm to room temperature with stirring over 1.5h. 1M Hydrochloric acid (50ml) was added and the mixture stirred vigorously for 1h. The organic layer was separated and the aqueous layer extracted with diethyl ether (50ml). The combined organic phase were washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The yellow oil was flash chromatographed (silica gel, 10-20% EtOAc-isohexane) to give the title compound as a clear oil (1.74g, 80%).
LC/MS RT = 3.28min [(2M-H_2O)H-] = 589.3

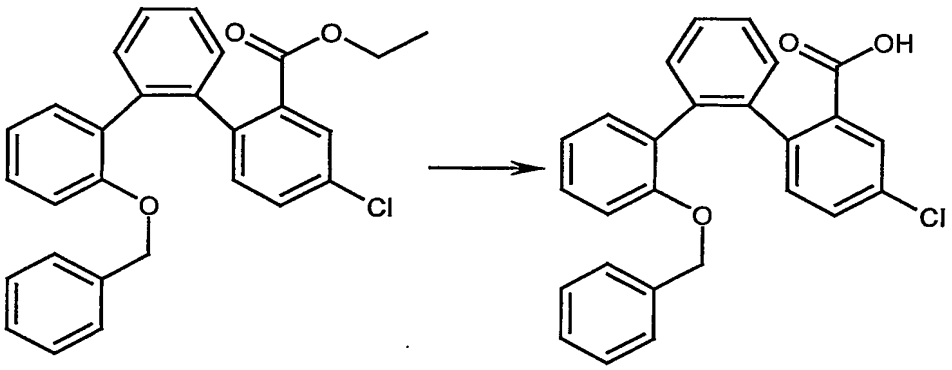
c) 2-Benzyloxy-4''-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester



A mixture of 2'-benzyloxy-biphenyl-2-boronic acid (61 mg,0.2 mmol), ethyl 2-bromo-5-chlorobenzoate (53 mg, 0.2 mmol), potassium carbonate (207 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol) in 1:1 toluene/ethanol (3 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ($MgSO_4$) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a colourless gum (63 mg, 71%).

^{1}H NMR ($CDCl_3$) δ: 0.97 (3H, br s), 3.99 (2H, br s), 4.87 (2H, br q), 6.75-6.81 (2H, m), 6.98-7.02 (2H, m), 7.14-7.41 (11H, m), 7.65 (1H, d, J=2Hz).

d) 2-Benzyloxy-4''-chloro[1,1';2',1'']terphenyl-2''-carboxylic acid



2-Benzyloxy-4"chloro-[1,1',2',1"]terphenyl-2"-carboxylic acid ethyl ester (58 mg, 0.137 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and heated at 75°C for 9 hours. The resulting solution was diluted with water, washed with iso-hexane and the aqueous suspension separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ($MgSO_4$) evaporated to dryness and triturated with iso-hexane/diethyl ether to yield the title compound as a white solid. (26 mg, 48%).

^{1}H NMR ($CDCl_3$) δ: 4.91 (2H, br d), 6.71 (1H, d, J=8Hz), 6.80-7.47 (14H, m), 7.69 (1H, d, J=2Hz).

LC/MS t=3.95, [MH-] 413, 415.

The following compounds were prepared in a similar manner:

Example 14: 2-Benzyloxy-5''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid

a) 2-Benzyloxy-5''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 0.94 (3H, br s), 3.98 (2H,br s), 4.90 (2H, br q), 6.76-6.79 (3H, m),6.85-7.42 (12H, m), 7.70 (1H, dd, J=9Hz).

b) 2-Benzyloxy-5''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 4.89 (2H, br q), 6.73 (2H, m), 6.80-7.45 (13H, m), 7.74 (1H, dd, J=9Hz).

LC/MS t=3.76, [MH-] 397.

Example 15: 2-Benzyloxy-4''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid

a) 2-Benzyloxy-4''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 0.96 (3H, br s), 3.99 (2H, br s), 4.88 (2H, br q), 6.76-6.78 (2H, m), 7.02-7.41(14H, m).

b) 2-Benzyloxy-4''-fluoro-[1,1';2',1'']terphenyl-2''-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 4.91 (2H, br d), 6.71 (1H, d, J=8Hz), 6.80-7.47 (15H, m).

LC/MS t=3.79, [MH-] 397.

Example 16: 2''-Benzyloxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid

a) 2''-Benzyloxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7Hz), 4.27 (2H, q, J=7Hz), 4.72 (2H, br d), 6.76 (1H, d, J=8Hz), 6.90-6.93 (2H, m), 7.04 (2H, d), 7.16-7.50 (10H, m), 7.63 (1H, s).

b) 2''-Benzyloxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 4.78 (2H br d), 6.77 (1H, d, J=8Hz), 6.92-7.06 (4H, m), 7.16-7.45 (9H, m), 7.56, (1H, d, J=8Hz), 7.69 (1H, s).

LC/MS t=3.98, [MH-] 397.1.

Example 17: 4''-Amino-2-benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid

a) 4''-Amino-2-benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

^{1}H NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7Hz), 4.18, (2H, q, J=7Hz), 5.62 (2H, br s), 6.39 (1H, d, J=8Hz), 6.75, (1H, d, J=8Hz), 6.86-6.96 (2H, m), 7.04 (1H, d, J=7Hz), 7.16-7.41 (10H, m), 7.71 (1H, d, J=2Hz).

LC/MS t=4.04, [MH+] 424.1.

b) 4''-Amino-2-benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid

^{1}H NMR ($CDCl_3$) δ: 4.82 (2H, br s), 5.65 (2H, br s), 6.39 (1H, d, J=8Hz), 6.76 (1H, d, J=8Hz), 6.91 (1H, t), 6.96 (1H, dd), 7.06 (2H, d, J=7Hz), 7.15-7.41 (9H, m), 7.77 (1H, d, J=2Hz).

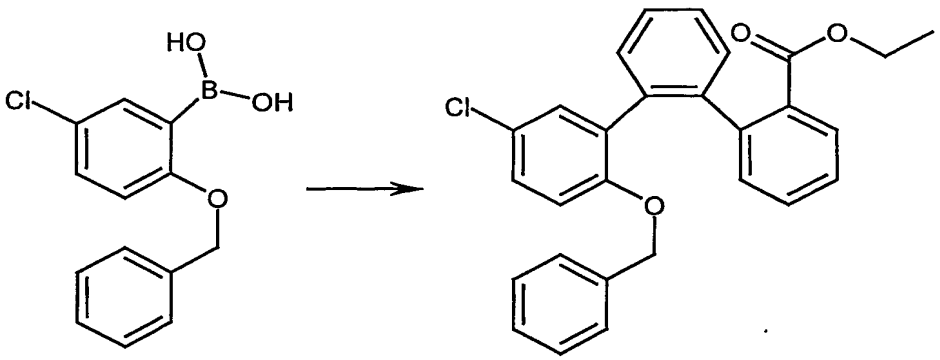
LC/MS t=3.72, [MH-] 394.2.

Example 18: 5''-Acetylamino-2-benzyloxy-[1,1';2',1'']terphenyl-2''-carboxylic acid

LC/MS t=3.38 [MH-] 436.

Example 19: 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid

a) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester



A mixture of 2'-benzyloxy-5'-chlorophenylboronic acid (947mg, 3.61mmol), 2'-Bromo-biphenyl-2-carboxylic acid ethyl ester (1.0g, 3.28 mmol), potassium carbonate(3.39g, 24.6mmol), and tetrakis(triphenylphosphine)palladium (0) (379mg, 0.32mmol) in1:1 toluene/ethanol (40ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl etherand water. The organic phase was dried and evaporated. The residue was chromatographed eluting with dichloromethane/iso-hexane (1:4 to 1:1) to yield the title compound as a colourless gum(1.28g, 88%).

^{1}H NMR ($CDCl_3$) δ:0.98(3H, br s), 4.09(2H, br s), 4.77(2H, m), 6.61(1H, d, J=9Hz), 7.0-7.4(14H, m), 7.69 (iH, d, J=8Hz).

LC/MS t=4.09.

b) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid

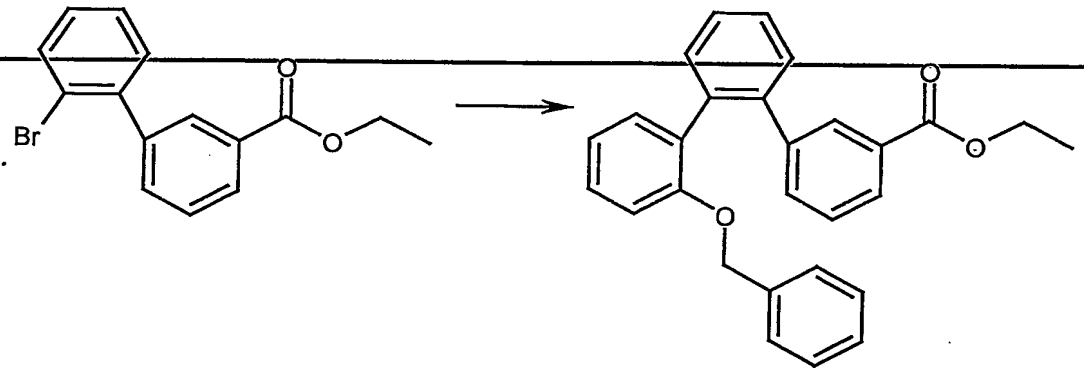
The title compound was prepared in a manner similar to 2-benzyloxy-4''-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid.

^{1}H NMR ($CDCl_3$) δ: 4.83(2H, m), 6.58(1H, d, J=9Hz), 6.95-7.33(14H, m), 7.75(1H, m)

LC/MS t=3.79, [MH-] 413.1,415.1(1xCl).

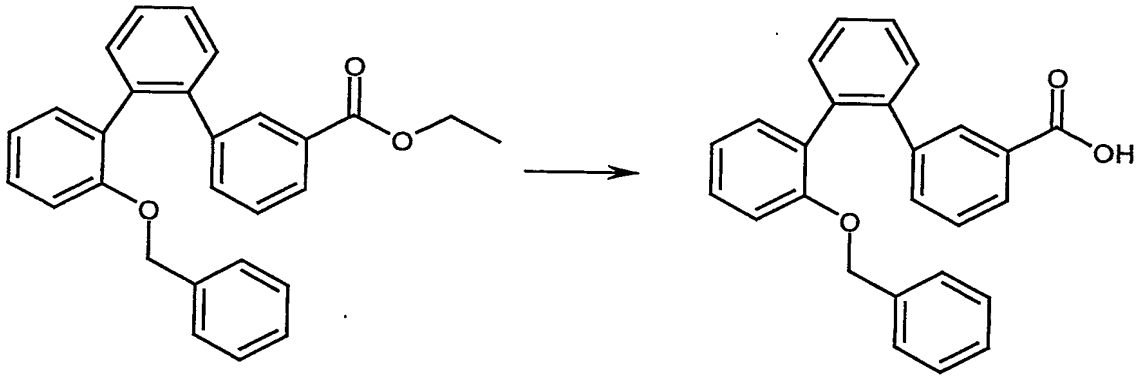
Example 20: 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic-acid

a) 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester



2'-Bromobiphenyl-3-carboxylic acid ethyl ester (153mg, 0.5mmol) and 2-benzyloxyphenylboronic acid (125mg (0.55mmol) were dissolved in 1:1 toluene:ethanol (5ml) under nitrogen. Potassium carbonate (552mg, 4mmol) and tetrakis(triphenylphosphine)palladium(0) (58mg, 0.05mmol) were added and the mixture heated at 90°C for 3 h. After cooling, the solvent was evaporated. The residue was partitioned between diethyl ether and water and the organic phase washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was flash chromatographed (silica gel, 2-10% EtOAc-isohexane) to give the title compound as a clear oil (84mg, 41%).
LC/MS RT = 4.09 [(M-OEt)H+] = 363.1.

b) 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid

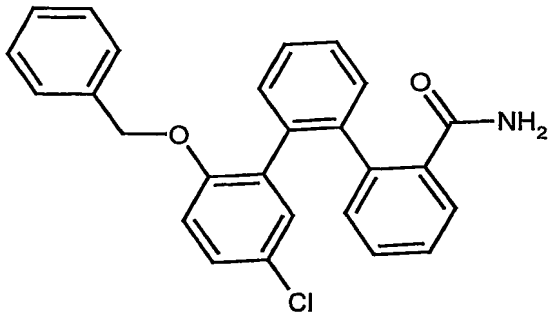


2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester (84mg, 0.206mmol) was dissolved in ethanol (2ml) and 2M sodium hydroxide (0.5ml) added. The mixture was stirred and heated to 50°C for 4h. Water was added and the mixture extracted with isohexane. The aqueous layer was acidified with 2M hydrochloric acid and extracted with diethyl ether (2 x 10ml). The combined organic phases were washed with water, dried ($MgSO_4$) and evaporated. The oil was triturated with

isohexane and the resulting white solid filtered, washed with isohexane and dried in vacuo. (42mg, 54%).

^{1}H NMR ($CDCl_3$) δ: 4.72 (2H, d (broad)), 6.73 (1H, d, J = 8Hz) 6.92 (1H, t, J = 7Hz), 7.03 (2H, d, J = 7Hz), 7.15-7.26 (7H, m), 7.44 (4H, m), 7.89 (1H, d, J = 8Hz), 7.92 (1H, s).

Example 21: 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid amide



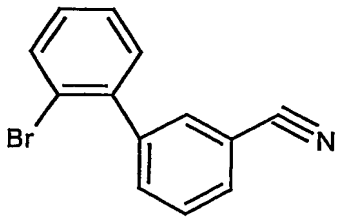
A solution of 2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-2"-carboxylic acid (100mg 0.24mmol) in toluene(1ml) containing DMF (5 drops) was treated with thionyl chloride (0.035ml, 0.48mmol) and heated at 90°C for 1 hour. After cooling to room temperature the sovent was evaporated. The residue was dissolved in tetrahydrofuran (1ml), aqueous ammonia (1ml)was added and the mixture stirred at room temperature for 3 hours. Addition of water (10ml) gave a precipitate which was filtered off and dried. (74mg 75%).

^{1}H NMR (DMSO-d_6) δ:5.09(2H,s) 6.75-7.47(18H, m).

LC/MS t=3.57 [MH+] 414.0,416.0(1 Cl).

Example 22: 5-(2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-yl)-1H-tetrazole

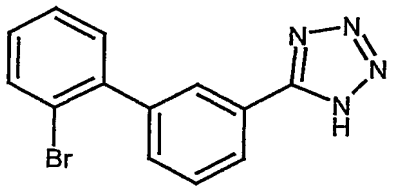
a) 2'-Bromo-biphenyl-3-carbonitrile



A mixture of 3-cyanophenylboronic acid (735 mg, 5 mmol), 1,2-dibromobenzene (2.36 g, 10 mmol) potassium carbonate (6.9 g, 50 mmol) and tetrakis(triphenylphosphine)palladium(0) (580 mg, 0.5 mmol) in 1:1 toluene/ethanol (40 ml) was stirred and heated at 90^{0}C under nitrogen for 3 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried

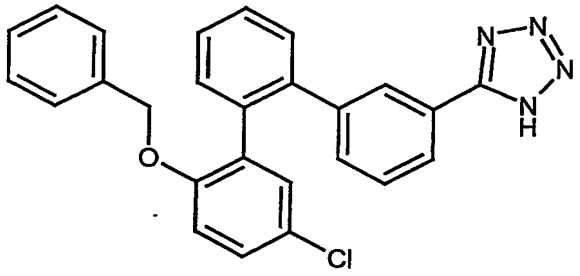
($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a white solid (895 mg 69%).
^1H NMR ($CDCl_3$) δ: 7.25-7.30 (3H, m), 7.40 (1H, t, J=7Hz), 7.54 (1H, t, J=7Hz), 7.65-7.71 (3H, m).

b) 5-(2'-Bromo-biphenyl-3-yl)-1H-tetrazole



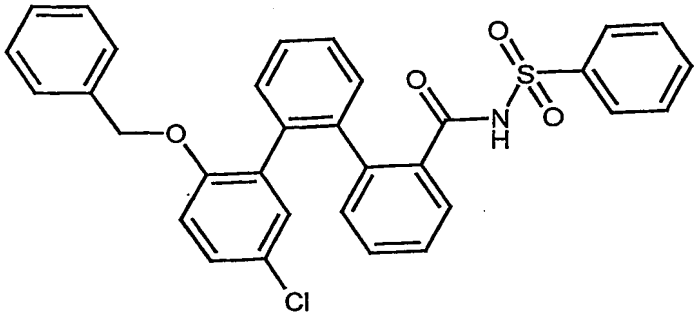
A mixture of 2'-bromo-biphenyl-3-carbonitrile (200mg,0.77mmol), sodium azide (66mg, 1.01mmol) and triethylamine hydrochloride(139mg, 1.01mmol) in toluene(2ml) was heated at 90°C for 24 hours. A further portion of sodium azide (66mg, 1.01mmol) and triethylamine hydrochloride (139mg, 1.01mmol) was added and heated for a further 24 hours. After cooling, the mixture was extracted with water (3x2ml). The combined extracts were acidified and the precipitate filtered off and dried. (163mg, 70%).
^1H NMR (DMSO-d_6) δ:7.38-7.80(6H, m), 8.06-8.11(2H,m).
LC/MS t=3.82 [MH-] 300.9 (1Br).

c) 5-(2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-yl)-1H-tetrazole



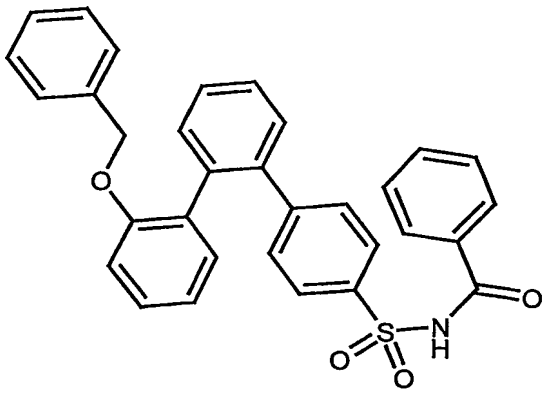
A mixture of 5-(2'-bromo-biphenyl-3-yl)-1H-tetrazole (163mg,0.54mmol), 2-benzyloxy-5-chlorobenzeneboronic acid (156mg, 0.59mmol), potassium carbonate (589mg, 4.33mmol), and tetrakis(triphenylphosphine)palladium(0) (63mg, 0.05mmol) in1:1 toluene/ethanol (5ml) was stirred and heated under nitrogen for 16 hours. After cooling the mixture was diluted with dichloromethane and water. The organic phase was dried and evaporated. The residue was chromatographed eluting with dichloromethane/methanol (95:5) to give the title compound as a colourless solid. (120mg 51%).
^1H NMR ($CDCl_3$) δ: 4.75 (2H, br s), 6.63 (1H, d, J=8Hz), 6.95-7.50 (14H, m), 7.88 (1H, m), 7.96 (1H, d, J=8Hz)
LC/MS t=4.22 [MH+] 439.0,441.0 (1 Cl).

Example 23: N-[1-(2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-yl)-methanoyl]-benzenesulfonamide



A mixture of 2-benzyloxy-5-chloro-[1,1';2',1"]terphenyl-2"-carboxylic acid (100mg, 0.24mmol), benzenesulphonamide (46mg, 0.29mmol), EDC (56mg, 0.29mmol), and 4-dimethylaminopyridine (5mg, 0.03mmol) in 1:1 dichloromethane/tetrahydrofuran(4ml) was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate(10ml) and washed with aq. sodium bicarbonate (5ml), dilute hydrochloric acid(5ml), water(5ml), and brine(5ml). the organic phase was dried and evaporated. Purification by prep. HPLC gave the title compound.(27mg 20%).
^{1}H NMR ($CDCl_3$) δ:5.12(2H, q, J=10Hz), 6.48(1H, d,J=6Hz), 6.6-7.8(19H, m), 9.23(1H, br s).
LC/MS t=3.98 [MH-] 552.2,554.2 (1 Cl).

Example 24: 2-Benzyloxy-[1,1';2',1'']terphenyl-4''-sulfonic acid (1-phenyl-methanoyl)-amide

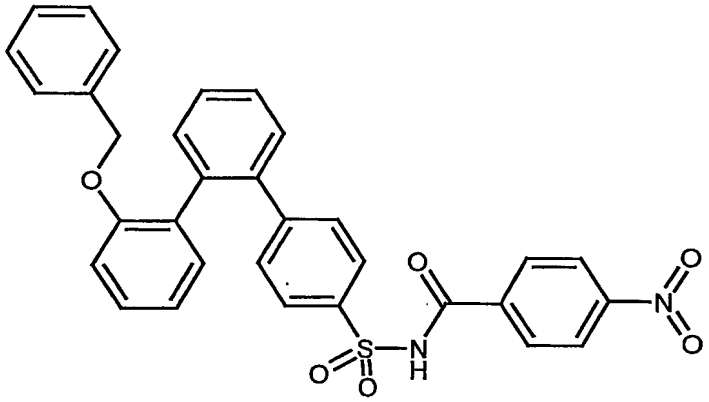


A mixture of 2'-benzyloxy-biphenyl-2-boronic acid (100mg, 0.33mmol), 4-bromo-N-(1-phenyl-methanoyl)-benzenesulfonamide (95mg, 0.28mmol), potassium carbonate (309mg, 2.24mmol), and tetrakis(triphenylphosphine)palladium(0) (38mg, 0.033mmol) in1:1 toluene/ethanol (5ml) was stirred and heated at 90°C under nitrogen for 16 hours. After cooling the mixture was diluted with ethyl acetate and water. The organic phase was dried and evaporated. The residue was chromatographed eluting with ethyl acetate/iso-hexane (1:4-1:1) to give the title compound as a colourless solid.(40mg 23%).

^{1}H NMR ($CDCl_3$) δ: 4.6(2H, br d), 6.64(1H, d,J=8Hz), 6.9-7.8(17H, m),7.79(2H, d, J=8Hz), 7.83(2H, d, J=8Hz), 9.0(1H, br s).
LC/MS t=4.09 [MH+] 520.1.

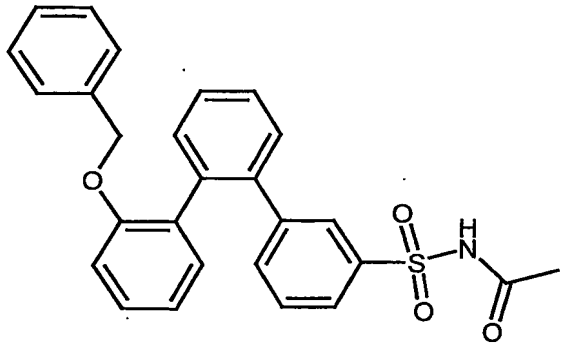
The following compounds were prepared in a similar manner:

Example 25: 2-Benzyloxy-[1,1';2',1'']terphenyl-4''-sulfonic acid [1-(4-nitro-phenyl)-methanoyl]-amide



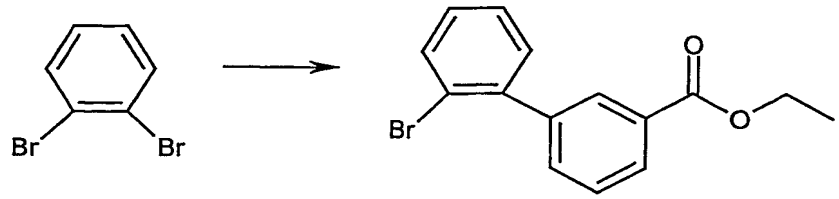
^{1}H NMR ($CDCl_3$) δ: 4.6(2H, br s), 6.59(1H, d, J=8Hz), 6.8-7.9(20H, m).
LC/MS t=4.57 [MH-] 563.

Example 26: 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-sulfonic acid acetyl-amide



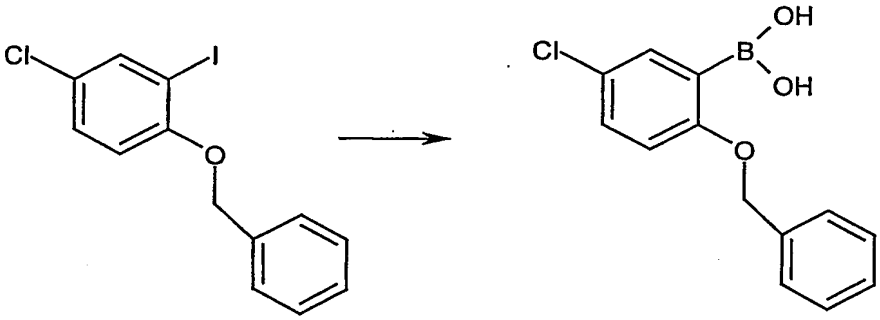
^{1}H NMR ($CDCl_3$) δ: 2.04(3H, s), 4.7(2H, br d), 6.70(1H, d, J=8Hz), 6.92-7.46(14H, m), 7.74(1H, s), 7.84(1H, d, J=8Hz), 8.1(1H, br s).
LC/MS t=3.64 [MH-] 456.

2'-Bromo-biphenyl-3-carboxylic acid ethyl ester



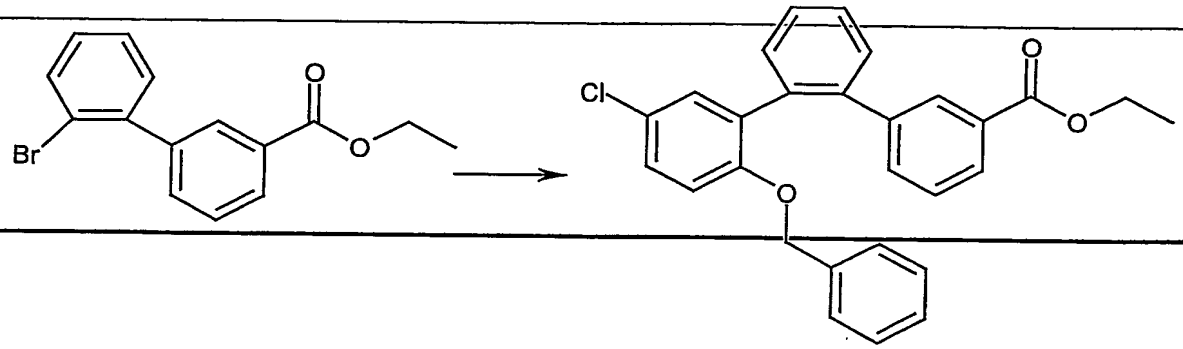
A mixture of 1,2-dibromobenzene (2.36g, 10.0 mmol), (3-ethoxylcarbonylphenyl) boronic acid (970mg, 5.0 mmol), tetrakis(triphenylphosphine)palladium (0) (580 mg, 0.50 mmol) and potassium carbonate (5.52g, 40 mmol) were heated in toluene-ethanol (1:1, 10ml) at 90°C for 3 hours. Upon cooling, the reaction mixture was poured into water and extracted with diethyl ether (3 x 100 ml); the organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Chromatographic purification using Biotage and 10% of ethyl acetate in iso-hexane as eluant gives a colourless oil (920 mg, 60%).
^1H NMR ($CDCl_3$) 1.4(3H,t,), 4.40(2H, q), 7.10-8.30(8H, m).

2-Benzyloxy-5-chloro-phenyl-boronic acid



Butyllithium(11.5 ml, 28.7 mmol, 2.5 M) was added, under nitrogen, over 10 minutes, to a solution of 2-benzyloxy-5-chloro-iodobenzene (9 g, 26.2 mmol) in THF (40 ml) at -100°C. The reaction mixture was then warmed up at -78°C and stirred for 1 hour (at -78°C) before triisopropyl borate (18 ml, 78.4 mmol) was added over 10 minutes. The reaction mixture was then warmed to room temperature before a solution of HCl (60 ml, 1M) was added. The mixture was vigorously stirred for 1 1/2 hours. The organic phase was separated , washed sequentially with water and brine, dried ($MgSO_4$) filtered and concentrated. The residue was triturated with a 30% solution of ether in iso-hexane and filtered to give the title compound (3.62g, 53%) as a white solid.
^1H NMR($CDCl_3$) 5.12(2H,s), 5.74(2H,s), 6.91(1H,d), 7.26(1H,s), 7,35-7.41(5H,m), 7.81(1H,s).

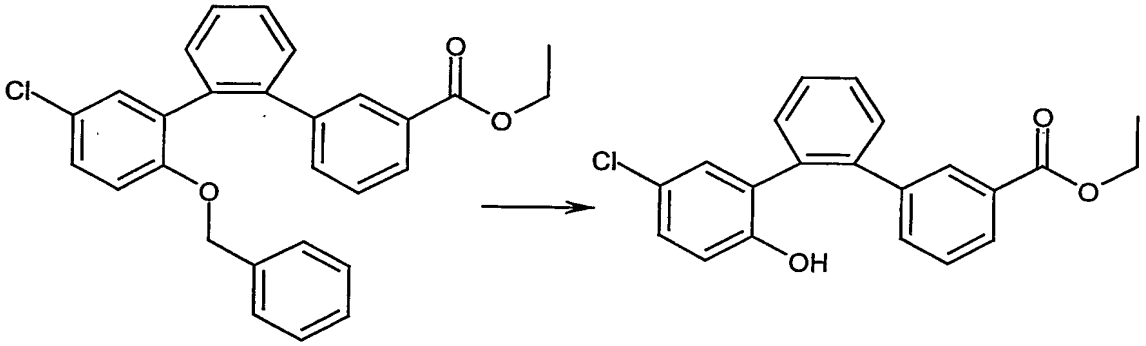
2-Benzyloxy-5-chloro-[1,1',2',1'']terphenyl-3''-carboxylic acid ethyl ester



2'-Bromo-biphenyl-3-carboxylic acid ethyl ester (920 mg, 3.0 mmol), 2-benzyloxy-5-chloro-phenyl-boronic acid (657 mg, 2.5 mmol), tetrakis(triphenylphosphine) palladium(0) (289 mg, 0.25 mmol) and potassium carbonate (2.77 g, 20.1 mmol) were heated in toluene-ethanol(1:1, 20 ml) at 90°C for 3 hours. Upon cooling, the mixture was diluted with diethyl ether and water, the combined organic layers were dried($MgSO_4$), filtered and concentrated. The residue was purified by chromatography using Biotage® with 10% ethyl acetate in iso-hexane as eluent to yeld the title compound (690 mg, 62%) as a white solid.

^1H NMR ($CDCl_3$) 1.32 (3H, t), 4.27(2H, q), 4.50-4.80(2H, br.s.), 6.60(1H, d), 6.96-7.88(15H, m).

5-Chloro-2-hydroxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

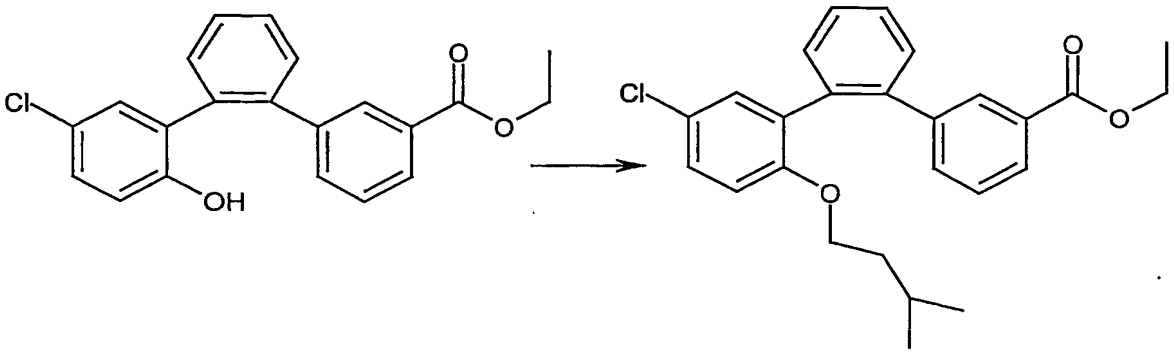


HBr(48% solution in acetic acid, 20 ml) was added to a solution of 2-benzyloxy-5-chloro-[1,1',2,2']terphenyl-3''-carboxylic acid ethyl ester (690 mg, 1.5 mmol) in acetic acid (4 ml). The reaction mixture was stirred at room temperature for 30 minutes, then diluted with water and extracted with ether. The organic phase was washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$) and evaporated. The residue was redissolved in ethanol and a 30% aqueous ammonia solution (2 ml) was added. The reaction mixture was stirred overnight, concentrated in vacuo to an oil that was purified by chromatography, using Biotage®, with 15% of ethyl acetate in iso-hexane to yield the title compound (340 mg, 62%) as a yellow solid.

^1H NMR ($CDCl_3$) 1.36 (3H, t), 4.33(2H, q), 6.68(1H, d), 7.08-7.93(10H, m).

A) General alkylation procedure

5-Chloro-2-(3-methyl-butoxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester



A mixture of 5-chloro-2-hydroxy-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester (50 mg, 0.14 mmol), potassium carbonate (48 mg, 0.35 mmol), and 1-bromo-3-methylbutane (23.5 mg, 0.15 mmol) was heated in N,N'-dimethylformamide (3 ml) at 90°C for 4 hours. The reaction mixture was then poured into water and extracted with ethyl acetate; the organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed through a SPE column using 10% ethyl acetate in iso-hexane as eluent to yeld the title compound as a white solid (45 mg, 75%). ^1H NMR($CDCl_3$) 0.76(6H, d),1.24-1.45 (6H,m) ,3.24-3.70(2H,br.) 4.32 (2H,br.q), 6.58(1H,d), 7.13-7.43(8H,m), 7.85(1H,d), 7.91(1H,s).

5-Chloro-2-cyclopentylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester
p-Toluenesulfonyl chloride(3.6 mmol, 684 mg) was added to a solution of cyclopentanemethanol (3 mmol, 300mg) and pyridine(3ml)in dichloromethane(3ml). The resulting mixture was stirred for 2 1/2 hours at room temperature, then diluted with dichloromethane and washed sequentially with HCl (1M solution) and a saturated solution of Na_2CO_3. The organic layer was then dried over $MgSO_4$ and evaporated to give the toluene-4-sulfonic acid cyclopentyl methyl ester. ^1H NMR ($CDCl_3$) 1.17(2H,m), 1.53(4H,m), 1.69(2H,m), 2.20(1H,m), 2.45(3H,s), 3.89(2H,d), 7.34(2H,d), 7.78(2H,d).

The general procedure A was employed to synthesise 5-chloro-2-cyclopentylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester using the toluene 4-sulfonic acid cyclopentyl methyl ester.

The following compounds were prepared following procedure A using the required bromide as alkylating agent (all commercially available). All the ^{1}HNMR spectra were recorded in $CDCl_3$ solution.

COMPOUND NAME	^{1}H NMR
5-chloro-2-(4-fluoro-benzyloxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.32(3H,t), 4.12(2H,br.q), 4.52-4.82(2H,br.d), 6.59(1H,d), 6.91(2H, d), 7.11-7.87(12H, m).
5-chloro-2-(2,4-difluoro-benzyloxy) -[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester	1.33(3H,t), 4.12(2H,br.q), 4.52-4.80(2H,br.d), 6.64 (1H,d), 6.70-7.87(13H,m).
5-chloro-2-(4-chloro-benzyloxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.31(3H,t), 4.26(2H,br.q), 4.42-4.78(2H,br.d), 6.56 (1H,d), 6.86(1H,d), 7.11-7.87(13H,m).
5-chloro-2-(2-fluoro-4-chloro-benzyloxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.32(3H,t), 4.12(2H,br.q), 4.45-4.81(2H,br.s), 6.61 (1H,d),6.74(1H,t), 6.99 (2H,t), 7.14-7.87(10H, m).
5-chloro-2-(4-isobutoxy)-[1,1',2',1"]terphenyl-3"-carboxylic acid ethyl ester	0.75(6H,d), 1.35(3H,t), 1.75-1.80(1H,m), 3.34(2H, br. s), 4.32(2H, q), 6.62(1H, d), 7.09-7.43(8H, m), 7.85(1H, d), 7.89(1H, s)
5-chloro-2-(pyridin-2-ylmethoxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.30(3H,t), 4.25(2H,q), 4.55-4.89(2H,br.s), 6.58(1H,d), 6.73(1H,d), 7.11-7.87(12H, m), 8.47(1H, d).
5-chloro-2-(pyridin-4-ylmethoxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.30(3H,t), 4.25(2H,br. s), 4.55-4.89(2H,br.d), 6.53(1H,d), 6.84(2H,d), 7.13-7.48(8H, m),7.80(1H,s), 7.86(1H,d) 8.46(2H, d).
5-chloro-2-(pyridin-3-ylmethoxy) -[1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.32(3H,t), 4.28(2H, br.q), 4.40-4.90(2H,br.d), 6.63 (1H,d) , 7.14-7.85(12H, m),8.30(1H, s) 8.49(1H, d).

5-chloro-2-cyclohexylmethoxy - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	0.75-1.72(14H, br. m), 3.28(2H,br.s), 4.32(2H,q), 6.62(1H,d), 7.11-7.44 (8H,m), 7.85(1H,d), 7.91(1H,s).
5-chloro-2-(thiophen-3-ylmethoxy) - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.33(3H,t), 4.28(2H, br.q), 4.50-4.82(2H,br.d), 6.64 (1H,d) , 6.75(1H, d), 6.84 (1H, d), 7.11-7.86(11H, m).
5-chloro-2-(thiophen-2-ylmethoxy) - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	1.34(3H,t), 4.30(2H,q), 4.71-4.84(2H,br.s), 6.71 (1H,d), 6.77-7.85(13H, m).
5-chloro-2-cyclopentylmethoxy - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	0.87-1.58(11H, m), 2.05 (1H,m), 3.46 (2H,br.s), 4.32(2H,q), 6.63 (1H,d), 7.08-7.43 (7H,m), 7.78 (1H,d), 7.85(1H,d), 7.90(1H, s).
5-chloro-2-propoxy - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	0.74(3H,t), 1.25(3H, t), 1.47 (2H,m), 3.30-3.75(2H, br.d), 4.31(2H,q), 6.58(1H, d), 7.11-7.43(8H,m), 7.85 (1H,s), 7.89(1H,s).
2-butoxy-5-chloro- [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	0.78(3H,t), 0.79-0.88 (1H,m), 1.15-1.21 (1H,m), 1.34(3H, t), 1.39-1.44 (2H,m), 3.29-3.75 (2H, br.d), 4.29(2H,q), 6.70 (1H, d), 7.08-7.42(8H,m), 7.79-7.83(2H,m).
5-chloro-2-isopropoxy - [1,1';2',1"]terphenyl-3"carboxylic acid ethyl ester	0.77-1.1(6H, br.s), 1.34(3H,t), 4.14(1H,m), 4.32(2H,q), 6.58(1H,d), 7.11-7.43(8H,m), 7.85(1H,d), 7.90(1H,s).

B) Mitsunobu reaction

5-Chloro-2-phenethyloxy-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester

A mixture of 5-chloro-2-hydroxy-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester(100 mg, 0.28 mmol), phenethyl alcohol (31 mg, 0.25 mmol), triphenyl phosphine(74 mg, 0.28 mmol), diisopropyl azodicarboxylate (57 mg, 0.28 mmol) in THF (6 ml) was stirred at room temperature overnight. The mixture was then poured into water and extracted with ether, the organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed through an SPE column using iso-hexane to yield the title compound (95mg, 80%) as an oil.

^1H NMR ($CDCl_3$) 1.32(3H,t), 2.74(2H,t), 3.41-3.92(2H, br. d),4.30(2H,q), 6.54(1H,d), 6.93-7.90(15H, m).

C) General procedure for ester deprotection

Example 27: 5-Chloro-2-(3-methyl-butoxy)-[1,1';2',1"]terphenyl-3"-carboxylic acid

5-Chloro-2-(3-methyl-butoxy)-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester(45mg,0.106 mmol) and NaOH (excess) were heated at 60°C in ethanol (3 ml) for 2 hrs. The mixture was then cooled to room temperature, diluted with water , acidified with HCl (1M solution) and extracted with ethyl acetate.The combined extracts were dried ($MgSO_4$) and evaporated to yeld the title compound (41 mg, 98%) as a white solid.

^1H NMR($CDCl_3$) 0.78(6H,d),1.35(2H,m),1.44-1.49(1H,m), 3.2-3.7(2H,br.s), 6.61(1H,d), 7.14-7.43(8H,m), 7.91(1H,d), 8.02(1H,s).

LC/MS R_t=4.13 min. *m/z* [MH^-] 393, 395

The following compounds of formula (I) were prepared by methods analogous to procedure C.

EXAMPLE	COMPOUND NAME	LC/MS	HNMR
28	5-chloro-2-(4-fluoro-benzyloxy) -[1,1';2',1"]terphenyl-3"carboxylic acid	R_t=3.97 min. [MH^-] 431,433	4.52-4.82 (2H,br.d), 6.61(1H,d), 6.92-7.90(14H, m).
29	5-chloro-2-(2,4-difluoro-benzyloxy) -[1,1';2',1"] terphenyl-3"-carboxylic acid	R_t=3.99 min. [MH^-] 449,451	4.52-4.80 (2H,br.s), 6.67 (1H,d), 6.69-7.50(11H,m),7.90(1H,s) ,7.93(1H,s)
30	5-chloro-2-(4-chloro-benzyloxy)-[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=4.12 min. [MH^-] 447,449	4.42-4.78(2H,br.d), 6.59 (1H,d), 6.90(1H,d), 7.12-7.92(13H,m).

31	5-chloro-2-(2-fluoro-4-chloro-benzyloxy) -[1,1';2',1"] terphenyl-3"carboxylic	R_t=4.15 min. [MH$^-$] 465,467	4.45-4.81(2H,br.s), 6.64 (1H,d),6.80(1H,t), 7.0(2H,d), 7.14-7.93(10H, m).
32	5-Chloro-2-(4-isobutoxy)-[1,1',2',1"] terphenyl-3"-carboxylic acid	R_t=4.05 min. [MH$^-$] 379,381	1.75-1.85(1H,m), 3.39(2H, br. s), 6.64(1H, d), 7.06-7.43 (8H, m), 7.90(1H, d), 7.99(1H, s)
33	5-chloro-2-(pyridin-2-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.61 min. [MH$^+$] 416,418	4.61(1H,br.s), 4.87(1H,br.s), 6.61(1H,d), 6.88(1H,d), 7.13-7.91(12H, m), 8.51(1H, br. s).
34	5-chloro-2-(pyridin-4-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.37 min. [MH$^+$] 416,418	
35	5-chloro-2-(pyridin-3-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.47 min. [MH$^+$] 416,418	4.19(1H,br. s), 4.79(1H,br.s), 6.62(1H,d), 7.06-7.88(12H, m) ,8.35(1H,br. s) 8.50(1H, br. s).
36	5-chloro-2-cyclohexylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid	R_t=4.33 min. [MH$^+$] 421	0.74-1.60(11H, br. m), 3.38(2H,br.s), 6.63(1H,d), 7.08-7.43 (8H,m), 7.91(1H,d), 8.02(1H,s).
37	5-chloro-2-(thiophen-3-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.91 min. [MH$^-$] 419,421	4.55-4.85(2H,br.d), 6.66(1H,d) , 6.76(1H, d), 6.87 (1H, s), 7.12-7.92(11H, m).
38	5-chloro-2-(thiophen-2-ylmethoxy) -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.89 min. [MH$^-$] 419,420	4.84(2H,br.s), 6.73 (1H,d), 6.79-7.92(13H, m).

39	5-chloro-2-cyclopentylmethoxy -[1,1';2',1"]terphenyl-3"carboxylic acid	R_t=4.22 min. [MH$^-$] 405,407	0.83-1.62(8H, br.m), 2.07(1H,m), 3.51 (2H,br.s), 6.65 (1H,d), 7.06-7.44 (8H,m), 7.90 (1H,d), 7.99(1H,s),
40	5-chloro-2-propoxy -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.92 min. [MH$^-$] 365,367	0.77(3H,t), 1.50 (2H,m), 3.30-3.70(2H, br.d), 6.61(1H, d), 7.13-7.44(8H,m), 7.90 (1H,s), 8.00(1H,s).
41	2-butoxy-5-chloro-[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=4.03 min. [MH$^-$] 379,381	0.81(3H,t), 1.16-1.25 (2H,m),1.42-1.49(2H,m), 3.29-3.75 (2H, br.s), 6.61(1H, d), 7.12-7.45(8H,m), 7.91(1H,s), 8.02(1H,s).
42	5-chloro-2-isopropoxy -[1,1';2',1"] terphenyl-3"carboxylic acid	R_t=3.87 min. [MH$^-$] 365,367	0.73-0.93(6H, br.s), 4.14(1H,m), 6.81(1H,d), 7.16-7.46(9H,m), 7.77(1H,br. s),

Example 43: 5-Chloro-2-isobutoxy-[1,1';2',1"]terphenyl-2"-carboxylic acid

a) 2'-Bromo-biphenyl-2-carboxylic acid ethyl ester

Prepared using the same conditions for the synthesis of 2'-bromo-biphenyl-3-carboxylic acid ethyl ester substituting 3-ethoxycarbonylphenyl boronic acid with 2-ethoxycarbonylphenylphenyl boronic acid.

^{1}H NMR ($CDCl_3$) 1.01 (3H, t, J=7Hz), 4.10 (2H, m), 7.19-7.26 (3H, m), 7.33 (1H, t, J=7Hz), 7.48 (1H, t, J=7Hz), 7.55-7..62 (2H, m), 8.04 (1H, d, J=8Hz).

b) 5-Chloro-2-hydroxy-[1,1';2',1"]terphenyl-2"-carboxylic acid ethyl ester

Prepared using the same conditions used for the synthesis of 5-chloro-2-hydroxy-[1,1';2',1"]terphenyl-3"-carboxylic acid ethyl ester except 2-benzyloxy-5-chloro-[1,1',2,2']terphenyl-2"-carboxylic acid ethyl ester was used instead of 2-benzyloxy-5-chloro-[1,1',2,2']terphenyl-3"-carboxylic acid ethyl ester.

^{1}H NMR ($CDCl_3$) 1.24 (3H, t), 4.23(2H, q), 6.59(1H, d), 7.04-7.47(9H, m), 7.82(1H,dd).

c) 5-Chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester

Prepared as in procedure A from 5-chloro-2-hydroxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester and 1-bromo-2-methyl-propane.

^{1}H NMR ($CDCl_3$) 0.85(6H,br. s), 1.04(3H,t), 1.91(1H,m), 3.49(2H, br. s), 4.07(2H, br. m), 6.63(1H, d), 7.03-7.37(9H, m), 7.71(1H, d).

d) 5-Chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid

Prepared as in procedure C from 5-chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester.

^{1}H NMR ($CDCl_3$) 0.78(6H,br. t), 1.88(1H, m), 3.49(2H, br. d), 6.63(1H, d), 7.07-7.41(9H,m), 7.79(1H,d).

LC/MS R_t=3.91(100%) [M^-] *m/z* 379,381.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10μg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a

medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

Binding Assay for the Human Prostanoid EP1 Receptor

Competition assay using [^{3}H]-PGE2

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E_2 ([^{3}H]-PGE_2) for binding to the human EP1 receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP_1 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10μg/ml puromycin and 10μM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na_2EDTA) and 10μM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na_2EDTA, 140mM NaCl, 10μM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na_2EDTA, 10mM $MgCl_2$ (pH 6). Aliquots are frozen at –80°C until required.

For the binding assay the cell membranes, competing compounds and [^{3}H]-PGE_2 (3nM final assay concentration) are incubated in a final volume of 100μl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding (IC_{50}).

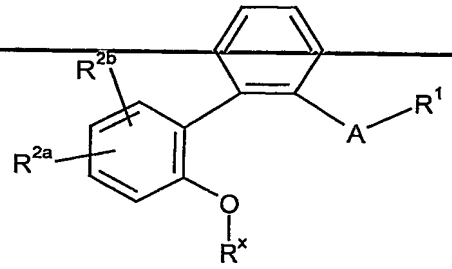
By application of these techniques, compounds of the examples had an antagonist pIC_{50} value of 6.0 to 9.0 at EP_1 receptors and pIC_{50} value of < 6.0 at EP_3 receptors.

No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A represents optionally substituted phenyl, an optionally substituted 5- or 6- membered heterocyclyl ring or an optionally substituted bicyclic heterocyclyl group;

R^1 represents hydrogen, CO_2R^4, $CONR^5R^6$, $CH_2CO_2R^4$, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkenyl, optionally substituted SO_2C_{1-6}alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, $CONR^5R^6$, 2*H*-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;

wherein when A is a 6-membered ring the R^1 and phenyl group are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 and phenyl group are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

R^{2a} and R^{2b} independently represent hydrogen, halo, CF_3, optionally substituted C_{1-6}alkyl, CN, SO_2R^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted C_{1-8}alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from NR^4, O or SO_n, wherein n is 0, 1 or 2; or R^x may be optionally substituted CQ_2-heterocyclyl or optionally substituted CQ_2Ph wherein Q is independently selected from H and CH_3;

R^4 represents hydrogen or an optionally substituted C_{1-6}alkyl;

R^5 represents hydrogen or an optionally substituted C_{1-6}alkyl;

R^6 represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted SO_2aryl, optionally substituted SO_2heterocyclyl group, CN or COR^7;

R^7 represents optionally substituted aryl or heteroaryl;

or pharmaceutically acceptable derivatives thereof.